

(19)

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10659664
12.15.03

(11)

EP 0 903 343 A1

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(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
24.03.1999 Bulletin 1999/12

(21) Application number: 98117153.1

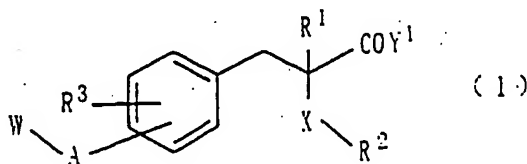
(22) Date of filing: 10.09.1998

(51) Int. Cl.⁶: C07D 237/32, C07D 239/88,
C07D 265/22, C07D 401/04,
C07D 239/96, C07D 243/08,
C07D 473/10, A61K 31/495(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 19.09.1997 JP 255025/97

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(54) Alpha-Substituted phenylpropionic acid derivative and medicine containing the same

(57) Disclosed herein are an α -substituted phenylpropionic acid derivative represented by the following general formula (1):

wherein W is a (substituted) lactam ring, A is an alkylene or alkyleneoxy group or the like, X is O, S, NH or CH₂, Y¹ is an amino, hydroxy or lower alkoxy group, R¹ is H, alkyl group or the like, R² is an alkyl or phenyl group or the like, and R³ is H, alkyl or alkoxy group or the like, or a salt thereof, and a medicine comprising such a compound as an active ingredient. The compound is excellent in the effect of lowering blood glucose and lipid.

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Description

BACKGROUND OF THE INVENTION

5 Field of the Invention:

[0001] The present invention relates to α -substituted phenylpropionic acid derivatives or salts thereof, which are excellent in the effect of lowering blood glucose and lipid, and medicines comprising such a compound as an active ingredient.

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Description of the Background Art:

[0002] Non-insulin dependent diabetes mellitus (NIDDM) is a disease caused by insulin resistance in a target tissue of insulin and impaired insulin secretion from β cells of pancreas. Sulfonylureas and insulin, which are in wide use for treating NIDDM at present, are agents for mainly improving impaired insulin secretion. Of these, the sulfonylureas, which are oral drugs, have a strong antidiabetic effect based on both pancreatic action and extrapancreatic action, but often cause serious hypoglycemia. Therefore, care must be taken in using them.

[0003] In recent years, the importance of insulin resistance in NIDDM has come to be indicated, so that there has been a demand for development of a drug exhibiting an antidiabetic effect by lightening insulin resistance in a target tissue of insulin without stimulating insulin secretion. As compounds having such an effect, have been developed thiazolidine derivatives such as troglitazone and pioglitazone (Japanese Patent Application Laid-Open Nos. 22636/1980, 51189/1985 and 157522/1994, etc.). In addition, some thiazolidine derivatives having a like effect and a bicyclic lactam structure or cyclic urethane structure have also been reported [Japanese Patent Application (KOHYO) Nos. 502144/1994, 502145/1994 and 502146/1994 (through PCT route), etc.]. Further, a great number of derivatives having no thiazolidine ring have also been reported [for example, Japanese Patent Application Laid-Open No. 170478/1991, Japanese Patent Application (KOHYO) No. 508054/1993 (through PCT route), etc.]. Furthermore, arylpropionic acid derivatives have also been reported as antidiabetics (WO91/19702, Japanese Patent Application Laid-Open Nos. 325250/1996, 325263/1996 and 325264/1996, etc.).

[0004] However, the blood glucose-lowering effect brought about by these compounds which lighten insulin resistance has been not yet sufficient.

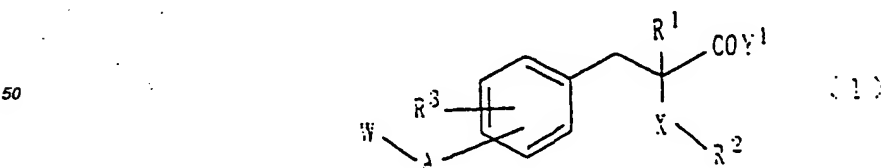
[0005] On the other hand, hyperlipemia and obesity have been becoming a problem in modern times when satiation and lack of exercise have been chronic, and there is hence a demand for development of medicines for treating these diseases.

35 SUMMARY OF THE INVENTION

[0006] Accordingly, it is an object of the present invention to provide a novel compound excellent in the effect of lowering blood glucose and lipid.

[0007] With the foregoing circumstances in view, the present inventors have synthesized various kinds of compounds and carried out an extensive investigation as to their pharmacological effects. As a result, it has been found that α -substituted phenylpropionic acid derivatives represented by a general formula (1), which will be described subsequently, are excellent in the effect of lowering blood glucose and lipid and hence are useful in preventing or treating diabetes mellitus, hyperlipemia, obesity and the like, thus leading to completion of the present invention.

[0008] According to the present invention, there is thus provided an α -substituted phenylpropionic acid derivative represented by the following general formula (1):



55 wherein W is a monocyclic or bicyclic lactam ring which may be substituted, A is an alkylene, alkyleneoxy or alkylene-carbonyl group which may be substituted by at least one hydroxy group, X is O, S, NH or CH₂, Y¹ is an amino, hydroxyamino, hydroxyalkylamino, monoalkylamino, dialkylamino, cyclic amino, hydroxy or lower alkoxy group, R¹ is a hydrogen atom, lower alkyl group, hydroxyalkyl group, alkoxyalkyl group, halogenoalkyl group or COY² (in which Y² is

an amino, hydroxyamino, hydroxyalkylamino, monoalkylamino, dialkylamino, cyclic amino, hydroxy or lower alkoxy group), R^2 is a lower alkyl, hydroxyalkyl, alkoxyalkyl or halogenoalkyl group, COY^2 (in which Y^2 has the same meaning as defined above), or a phenyl, pyridyl or aralkyl group which may be substituted, and R^3 is a hydrogen or halogen atom, or an alkyl, alkoxy, halogenoalkyl, amino, hydroxy or acyl group, or a salt thereof.

5 [0009] According to the present invention, there is also provided a medicine comprising the α -substituted phenylpropionic acid derivative represented by the general formula (1) or the salt thereof as an active ingredient.

[0010] According to the present invention, there is further provided a medicinal composition comprising the α -substituted phenylpropionic acid derivative represented by the general formula (1) or the salt thereof and a pharmaceutically acceptable carrier.

10 [0011] According to the present invention, there is still further provided use of the α -substituted phenylpropionic acid derivative represented by the general formula (1) or the salt thereof for a medicine.

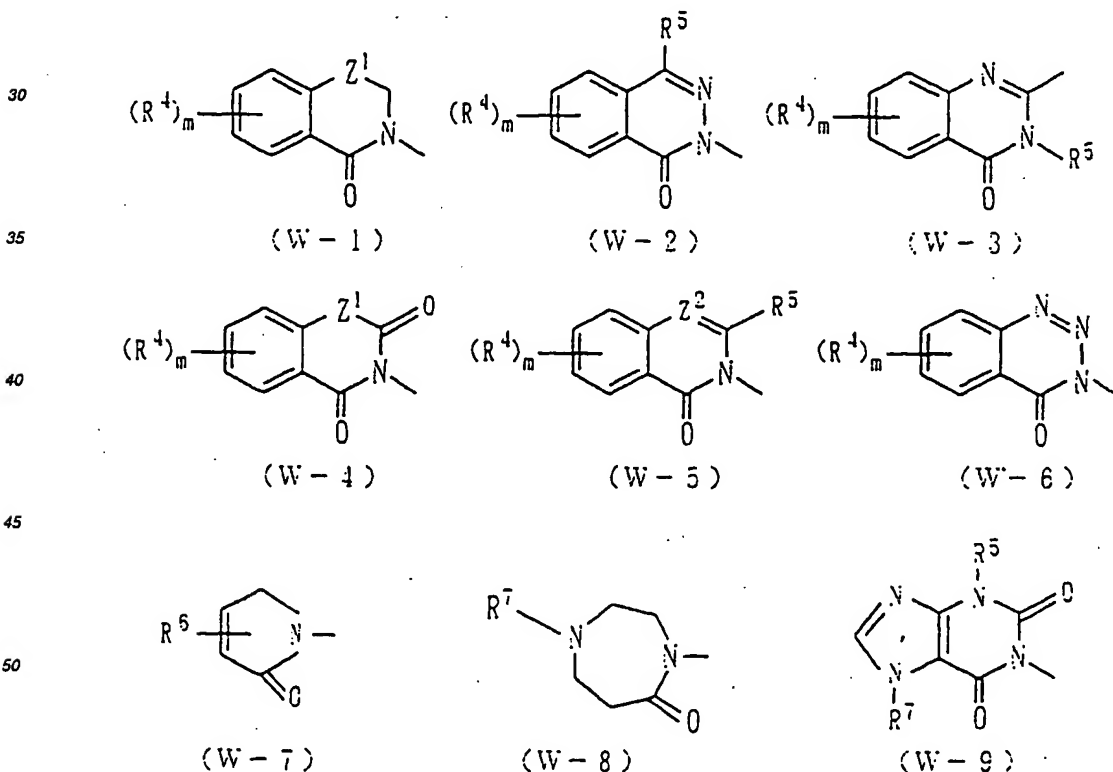
[0012] According to the present invention, there is yet still further provided a method of treating diabetes mellitus and/or hyperlipemia, which comprises administering the α -substituted phenylpropionic acid derivative represented by the general formula (1) or the salt thereof to a patient.

15 [0013] The compounds (1) according to the present invention are excellent in the effect of lowering blood glucose and lipid and are hence useful as agents for preventing or treating diabetes mellitus, hyperlipemia, obesity and the like.

[0014] The above and other objects, features and advantages of the present invention will be readily appreciated as the same becomes better understood from the preferred embodiments of the present invention, which will be described subsequently in detail, and from the appended claims.

20 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] The lactam ring represented by W in the α -substituted phenylpropionic acid derivatives according to the present invention, which are represented by the general formula (1), is preferably selected from among, for example,



wherein R^4 is a hydrogen or halogen atom, an alkyl, alkoxy, halogenoalkyl, amino, hydroxy, cyano, carbamoyl, acyl, nitro, carboxy or sulfonamide group, or a phenyl or benzyloxy which may be substituted, R^5 is a hydrogen atom, an alkyl

group, or an aryl, aralkyl or pyridyl group which may be substituted, R^6 is a hydrogen atom or a lower alkyl group, R^7 is a lower alkyl, phenyl or aralkyl group, Z^1 is O, S, CH_2 or NR^5 (in which R^5 has the same meaning as defined above), Z^2 is N or CH, and m is an integer of 1 to 4.

[0016] In the above formulae, the alkyl groups represented by R^4 and R^5 are preferably linear or branched alkyl groups having 1 to 8 carbon atoms. Examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl and octyl groups. The alkoxy group represented by R^4 is preferably a linear or branched alkoxy group having 1 to 8 carbon atoms. Examples thereof include methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy and octyloxy groups. Examples of the halogen atom include fluorine, chlorine, bromine and iodine atoms. The halogenoalkyl group is preferably an alkyl group substituted by 1 to 3 halogen atoms and having 1 to 8 carbon atoms. Examples thereof include trifluoromethyl, trichloromethyl and tribromomethyl groups. Examples of the acyl group include alkanoyl groups having 1 to 9 carbon atoms, such as formyl, acetyl and propionyl groups, and aroyl groups such as a benzoyl group. Examples of substituents on the phenyl or benzyloxy group include the alkyl groups, alkoxy groups, halogen atoms, halogenoalkyl groups and acyl group, which have been mentioned above, and besides amino, hydroxy, cyano, carbamoyl, nitro, carboxy, sulfonamide, phenyl and benzyloxy groups.

[0017] The lower alkyl groups represented by R^6 and R^7 are preferably linear or branched alkyl groups having 1 to 6 carbon atoms. Examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and sec-butyl groups. Examples of the aryl group represented by R^5 include aryl groups having 6 to 14 carbon atoms, such as phenyl and naphthyl groups. Examples of the aralkyl groups represented by R^5 and R^7 include phenyl- C_{1-6} -alkyl groups such as benzyl and phenethyl groups. Examples of substituents on the aryl, aralkyl or pyridyl group represented by R^5 include the same substituents as those mentioned in the phenyl group represented by R^4 . The group W is particularly preferably (W-1), (W-2) (W-4) or (W-5).

[0018] The group A in the general formula (1) is preferably a linear or branched alkylene group having 1 to 8 carbon atoms, which may be substituted by 1 to 5 hydroxy groups, a linear or branched alkyleneoxy group having 1 to 8 carbon atoms, which may be substituted by 1 to 5 hydroxy groups, or a linear or branched alkylene carbonyl group having 2 to 9 carbon atoms, which may be substituted by 1 to 5 hydroxy groups. Specific examples of A include ethylene, trimethylene, propylene, tetramethylene, butylene, ethyleneoxy, trimethyleneoxy, 2-hydroxytrimethyleneoxy, propyleneoxy, butyleneoxy, methylenecarbonyl, ethylenecarbonyl and trimethylenecarbonyl groups. Of these, the ethylene, trimethylene, ethyleneoxy and 2-hydroxytrimethyleneoxy groups are particularly preferred.

[0019] An atomic group represented by X is preferably an oxygen atom.

[0020] With respect to the groups represented by Y^1 and Y^2 , the alkyl moieties of the mono- or dialkylamino groups or hydroxyalkylamino groups are linear or branched alkyl groups having 1 to 6 carbon atoms. Examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl groups. Examples of the cyclic amino groups include 4-membered to 7-membered cyclic amino groups such as piperazinyl, piperidinyl, pyrrolidinyl and azetidinyl groups. Examples of the alkoxy groups include linear or branched alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy and butoxy groups.

[0021] Examples of the lower alkyl groups represented by R^1 and R^2 include linear or branched alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl groups.

[0022] The hydroxyalkyl group represented by R^2 is preferably a hydroxy- C_{1-6} -alkyl group. Examples thereof include hydroxyethyl and hydroxypropyl groups. The alkoxyalkyl group represented by R^2 is preferably a C_{1-6} -alkoxy- C_{1-6} -alkyl group. Examples thereof include methoxyethyl, ethoxyethyl and methoxypropyl groups. The halogenoalkyl group represented by R^2 is preferably an alkyl group substituted by 1 to 3 halogen atoms and having 1 to 6 carbon atoms. Examples thereof include trifluoromethyl and trifluoroethyl groups.

[0023] Examples of the aralkyl group represented by R^2 include phenyl- C_{1-6} -alkyl groups such as benzyl and phenethyl groups. Examples of substituents on the phenyl, pyridyl or aralkyl group represented by R^2 include alkyl groups, alkoxy groups, halogen atoms, halogenoalkyl groups, acyl groups, amino group, hydroxy group, cyano group, carbamoyl group, nitro group, carboxy group, sulfonamide group, phenyl group and benzyloxy group. R^1 is preferably a hydrogen atom. R^2 is preferably a lower alkyl group.

[0024] The alkyl group represented by R^3 is preferably a linear or branched alkyl group having 1 to 8 carbon atoms. Examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl and octyl groups. The alkoxy group represented by R^3 is preferably a linear or branched alkoxy group having 1 to 8 carbon atoms. Examples thereof include methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy and octyloxy groups. Examples of the halogen atom include fluorine, chlorine, bromine and iodine atoms. The halogenoalkyl group is preferably an alkyl group substituted by 1 to 3 halogen atoms and having 1 to 8 carbon atoms. Examples thereof include trifluoromethyl, trichloromethyl and tribromomethyl groups. Examples of the acyl group include alkanoyl groups having 1 to 9 carbon atoms, such as formyl, acetyl and propionyl groups, and aroyl groups such as a benzoyl group. R^3 is preferably a hydrogen atom.

[0025] The compounds (1) according to the present invention may include various kinds of pharmaceutically acceptable solvates such as hydrates, and those of polymorphism. Since the compounds (1) according to the present inven-

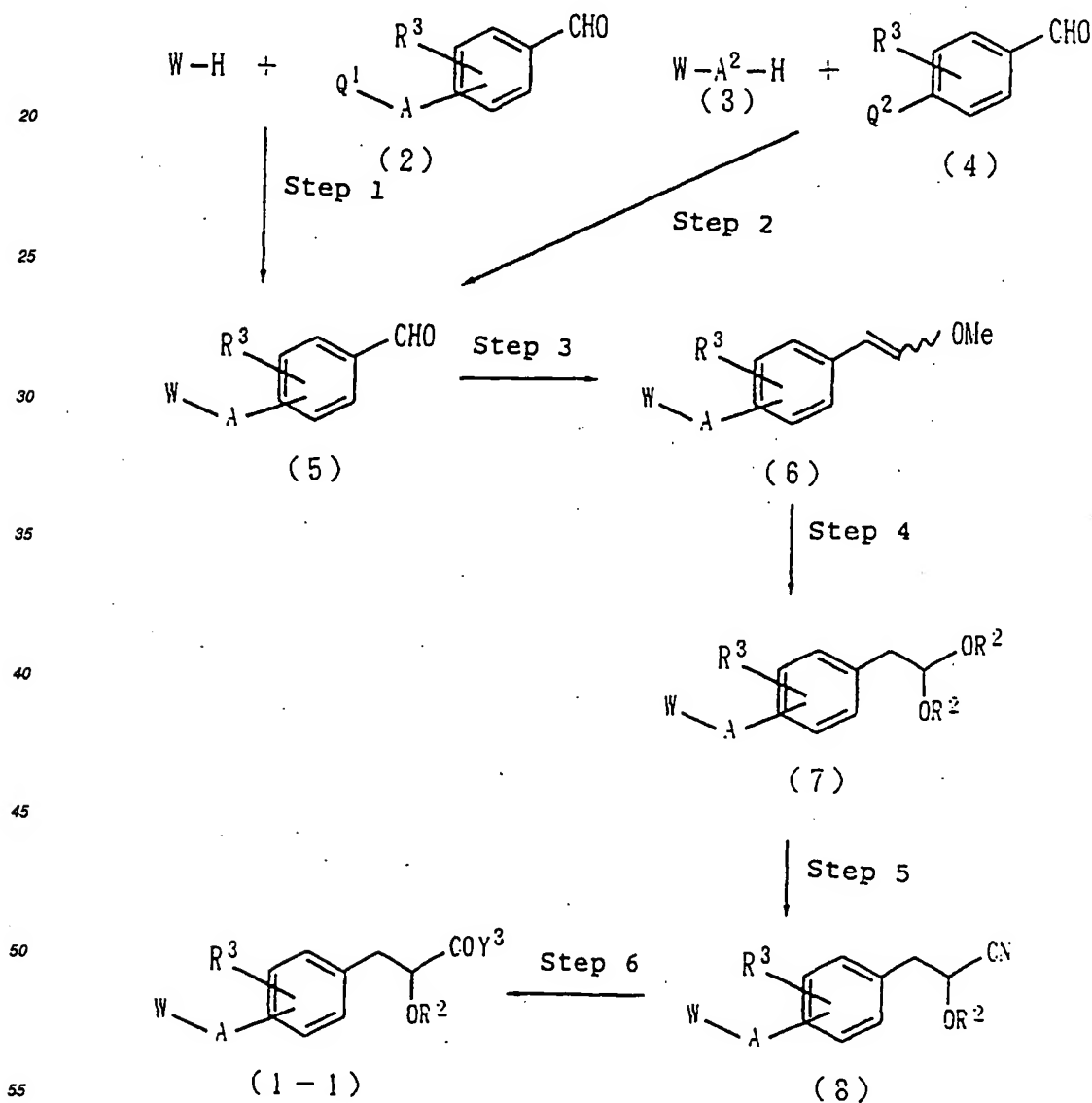
tion have an asymmetric carbon atom, stereoisomers exist. All these isomers are included in the present invention.

[0026] No particular limitation is imposed on salts of the compounds (1) according to the present invention so far as they are pharmaceutically acceptable salts. Preferable examples of such salts include hydrogen halide salts such as hydrofluorides, hydrochlorides, hydrobromides and hydriodides; inorganic acid salts such as carbonates, nitrates, perchlorates, sulfates and phosphates; lower alkyl-sulfonates such as methanesulfonates, ethanesulfonates and trifluoromethanesulfonates; arylsulfonates such as benzenesulfonates and p-toluenesulfonates; organic acid salts such as fumarates, maleates, succinates, citrates, tartrates and oxalates; amino acid salts such as glutamates and aspartates; and salts with alkali and alkaline earth metals such as sodium, potassium and calcium.

[0027] The compounds (1) according to the present invention can be prepared, for example, in accordance with any of the following Preparation Processes 1 to 8.

<Preparation Process 1>

Case of $R^1 = H$ and $X = O$ in the general formula (1):



wherein R^2 , R^3 , W and A have the same meanings as defined above, A^2 is an alkyleneoxy group which may be substi-

tuted by at least one hydroxyl group, Y^3 is an amino, hydroxyl or lower alkyl group, Q^1 is a leaving group, and Q^2 is a halogen atom.

[0028] More specifically, a compound (1-1) according to the present invention is prepared in the following manner. A compound represented by a general formula (2) is reacted with a compound represented by a general formula W-H to form a compound represented by a general formula (5) (Step 1). The 4-substitution product of compounds (5) may also be synthesized by the reaction of a compound represented by a general formula (3) with a compound represented by a general formula (4) (Step 2). The compound (5) is then subjected to a Wittig reaction with (methoxymethyl)triphenylphosphonium chloride (Step 3), and the resultant compound represented by a general formula (6) is reacted with its corresponding alcohol to form an acetal derivative represented by a general formula (7) (Step 4). The acetal derivative is then reacted with trimethylsilyl nitrile to form a compound represented by a general formula (8) (Step 5). Finally, the compound (8) is hydrolyzed or reacted with an alcohol in the presence of an acid catalyst (Step 6), whereby the compound (1-1) according to the present invention can be prepared. The individual steps will hereinafter be described in detail.

15 Step 1:

[0029] The compound (2) is reacted with the compound W-H in the presence of proper base and solvent, whereby the compound (5) can be obtained.

[0030] The compound (2) can be prepared by halogenation or sulfonylation of the terminal hydroxy group in the benzaldehyde derivative substituted by a hydroxyalkoxy group or hydroxyalkyl group, which has been purchased as a commercially available reagent or synthesized in accordance with a known method [for example, a method described in Journal of Heterocyclic Chemistry, 6, 243 (1969) or Japanese Patent Application Laid-Open No. 92228/1996]. Examples of the leaving group (Q^1) thereof include halogen atoms such as chlorine, bromine and iodine atoms, and methanesulfonyloxy, p-toluenesulfonyloxy and trifluoromethanesulfonyloxy groups. Of these, the methanesulfonyloxy group is particularly preferred.

[0031] Examples of the base used in the reaction of the compound (2) with the compound W-H include sodium hydride, calcium hydride, potassium t-butoxide, sodium hydroxide, potassium hydroxide and potassium carbonate. No particular limitation is imposed on the solvent used herein so far as it does not affect the reaction. Examples of the solvent used include ethers such as tetrahydrofuran and dioxane; hydrocarbons such as benzene and toluene; amides such as dimethylformamide, dimethylacetamide and N-methyl- α -pyrrolidone; and sulfoxides such as dimethyl sulfoxide. The reaction is carried out in a temperature range of from a temperature under ice cooling to a reflux temperature under heating. It is particularly preferred to conduct the reaction by heating and stirring the reactants at 70 to 100°C for 2 to 5 hours in the presence of potassium carbonate in dimethylformamide.

35 Step 2:

[0032] The compound (3) which is a starting material can be prepared, for example, in accordance with the method described in Journal of Medicinal Chemistry, 11, 1038 (1968); or Journal of Medicinal Chemistry, 38, 130 (1995). This compound (3) is reacted with the p-halogenobenzaldehyde derivative (4) in the presence of proper base and solvent, whereby the compound (5) can be obtained. Examples of the halogen atom Q^2 in the a p-halogenobenzaldehyde derivative (4) include, fluorine, chlorine, bromine and iodine atoms, with the fluorine atom being particularly preferred. Examples of the base used in this reaction include sodium hydride, potassium t-butoxide, sodium hydroxide and potassium hydroxide. No particular limitation is imposed on the solvent used herein so far as it does not affect the reaction. Examples of the solvent used include ethers such as tetrahydrofuran and dioxane; hydrocarbons such as benzene and toluene; amides such as dimethylformamide, dimethylacetamide and N-methyl- α -pyrrolidone; and sulfoxides such as dimethyl sulfoxide. The reaction is carried out in a temperature range of from a temperature under ice cooling to a reflux temperature under heating. The reaction time is about 0.5 to 24 hours. It is particularly preferred to conduct the reaction by adding sodium hydride little by little to a dimethyl sulfoxide solution of a mixture of the compound (3) and the compound (4) under ice cooling and then stirring the resultant mixture for 1 to 3 hours at room temperature or so.

50 Step 3:

[0033] The compound (5) is subjected to the Wittig reaction with (methoxymethyl)triphenylphosphonium chloride, which is a commercially available reagent, in the presence of proper base and solvent, whereby the compound (6) can be obtained [the compound (6) is obtained as a mixture of E:Z]. Examples of the base used in this reaction include n-butyllithium, sec-butyllithium, lithium diisopropylamide, potassium t-butoxide and sodium methoxide. No particular limitation is imposed on the solvent used herein so far as it does not affect the reaction. Examples thereof include ethers such as diethyl ether and tetrahydrofuran; hydrocarbons such as benzene and toluene; and alcohols such as ethanol.

It is particularly preferred to conduct the reaction by preparing lithium diisopropylamide in a flask containing tetrahydrofuran and stirring the reaction mixture at a reaction temperature of from -10°C to 20°C for about 3 to 5 hours.

Step 4:

[0034] The compound (6) is reacted with its corresponding alcohol in the presence of an acid catalyst, whereby the compound (7) can be prepared.

[0035] When the alcohol has a low boiling point, the alcohol itself is used as a solvent. When the alcohol has a high boiling point on the other hand, a hydrocarbon such as benzene or toluene, or an amide such as dimethylformamide or dimethylacetamide may be used as a solvent. Examples of the acid catalyst include p-toluenesulfonic acid and methanesulfonic acid. The reaction is carried out in a temperature range of from a warming temperature to a reflux temperature under heating. The reaction time is about 1 to 24 hours.

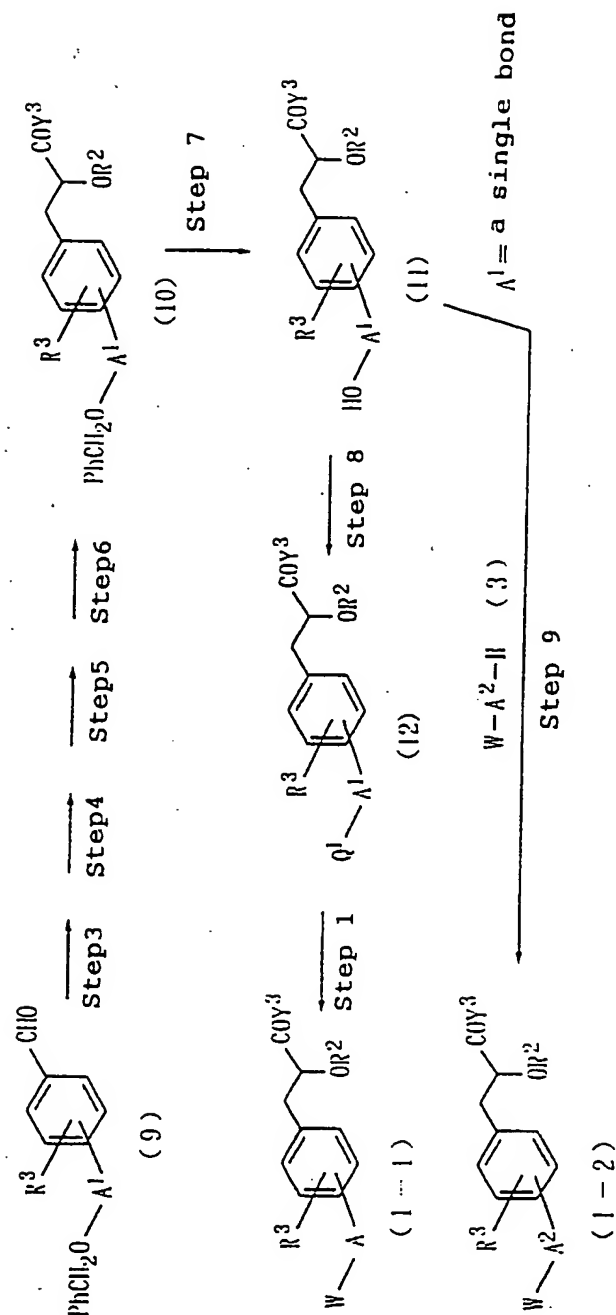
Step 5:

[0036] The compound (7) is reacted with an excess amount of trimethylsilyl nitrile in the presence of a boron trifluoride etherate catalyst in methylene chloride, whereby the compound (8) can be prepared. The reaction is carried out at a temperature of from 0 to 20°C for about 0.5 to 2 hours.

Step 6:

[0037] In general, the compound (8) is hydrolyzed under basic conditions, whereby the compound (1-1) according to the present invention can be prepared. Examples of the base used include sodium hydroxide and potassium hydroxide. As a solvent for the reaction, is used a mixed solvent of ethanol-water, dioxane-water or the like. The reaction is carried out in a temperature range of from 80°C to a reflux temperature for about 0.5 to 5 hours. An ester derivative corresponding to the compound (1-1) can be prepared by using a compound in which Y³ in the compound (1-1) according to the present invention is NH₂, and heating this compound and an alcohol with stirring in the presence of a catalytic amount of a Lewis acid such as titanium tetrachloride in 1N hydrochloric acid.

<Preparation Process 2> Case of $R^1 = H$ and $X = O$ in the general formula (1):



wherein W , R^2 , R^3 , Y^3 , A , A^2 and Q^1 have the same meanings as defined above, and A^1 means A or a single bond.

[0038] More specifically, a benzaldehyde derivative represented by a general formula (9) is allowed to react in the same manner as in Step 3 to Step 6 described in Preparation Process 1 to form a compound represented by a general formula (10). The benzyl group which is a protecting group is then removed from the compound (10) to obtain a com-

pound represented by a general formula (11) (Step 7). After the terminal hydroxy group of this compound is converted into a leaving group (Q^1) (Step 8), the resultant compound is allowed to react in the same manner as in Step 1 of Preparation Process 1, whereby the compound (1-1) according to the present invention can be prepared. When A^1 in the compound represented by the general formula (11) is a single bond, the compound is subjected to a condensation reaction with a compound represented by the general formula (3), whereby a compound (1-2) according to the present invention can be obtained (step 9). The individual steps will hereinafter be described.

Step 7:

[0039] The compound (9), which is a starting material, is purchased as a commercially available reagent or synthesized in accordance with a known method [for example, a method described in Journal of Heterocyclic Chemistry, 6, 243 (1969) or Japanese Patent Application Laid-Open No. 92228/1996], and is converted into a compound of the general formula (10) in the same manner as in Step 3 to Step 6 described in Preparation Process 1. This compound (10) is reduced by catalytical hydrogenation, whereby the compound of the general formula (11) can be prepared. Examples of the catalyst used in this reaction include palladium catalysts such as palladium on charcoal, palladium black and palladium hydroxide; platinum catalysts such as platinum oxide and platinum black; and nickel catalysts such as Raney nickel. No particular limitation is imposed on a solvent used so far as it does not affect the reaction. Examples thereof include methanol, ethanol, dioxane, dimethylformamide, acetic acid and a mixed solvent of ethanol-acetic acid. The reaction is carried out at atmospheric pressure or under pressure at room temperature or under heating at about 60 to 100°C.

Step 8:

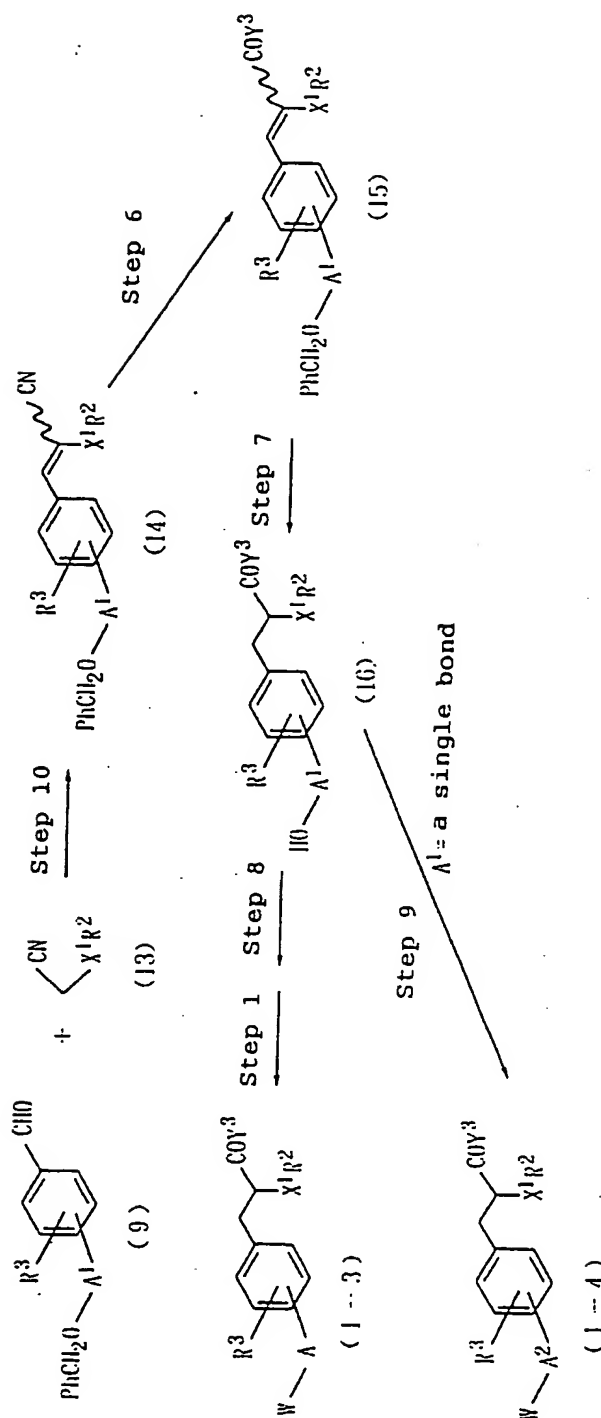
[0040] The compound (12) is prepared by halogenating or sulfonylating the terminal hydroxy group of the phenylpropionic acid derivative (11), the benzene ring of which has been substituted by a hydroxyalkoxy group, hydroxyalkyl group or hydroxyalkanoyl group, in the presence or absence of a base and a solvent. Examples of the leaving group (Q^1) thereof include halogen atoms such as chlorine, bromine and iodine atoms, and methanesulfonyloxy, p-toluenesulfonyloxy and trifluoromethanesulfonyloxy groups. Of these, the methanesulfonyloxy group is particularly preferred. No particular limitation is imposed on the solvent used in the reaction so far as it does not affect the reaction. Examples of the solvent used include chlorinated hydrocarbons such as methylene chloride and chloroform; ethers such as tetrahydrofuran and dioxane; hydrocarbons such as benzene and toluene; amides such as dimethylformamide, dimethylacetamide and N-methyl- α -pyrrolidone; and sulfoxides such as dimethyl sulfoxide. Examples of the base used include triethylamine, pyridine, 4-dimethylaminopyridine, sodium hydride, sodium hydroxide and sodium carbonate.

[0041] The compound (12) thus obtained can be converted into the compound (1-1) according to the present invention in the same manner as in Step 1 of Preparation Process 1.

Step 9:

[0042] Among the compounds represented by the general formula (11), a compound in which A^1 is a single bond can be converted into the compound (1-2) according to the present invention by a Mitsunobu reaction (see Organic Reaction 42, 335) with a compound represented by the general formula (3), which has been described in Preparation Process 1. More specifically, each 1 to 3 equivalents of triphenylphosphine and dialkyl (dimethyl, diethyl or diisopropyl) azobiscarboxylate are added to a solution of the compound (3) and compound (11) in methylene chloride, tetrahydrofuran, benzene, toluene, ether, dioxane or dimethylformamide, and the reaction is conducted in a temperature range of from -5°C to a reflux temperature under heating for about 1 to 24 hours, whereby the compound (1-2) according to the present invention can be obtained.

<Preparation Process 3> Case of $R^1 = H$ in the general formula (1):



wherein W , A , R^2 , R^3 , A^1 , A^2 and Y^3 have the same meanings as defined above, and X^1 is O , S or CH_2 .

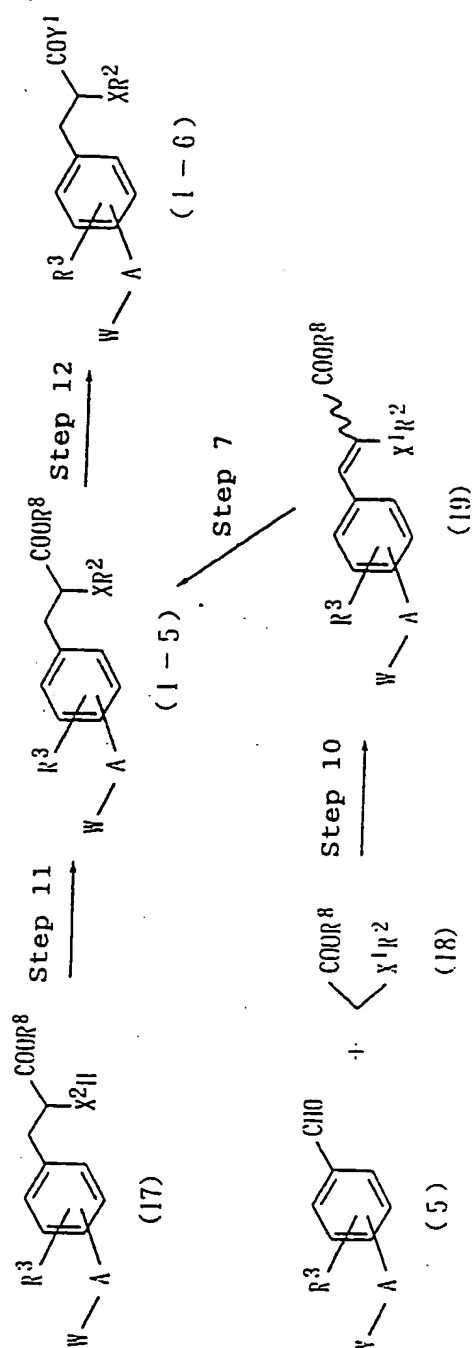
[0043] A compound represented by the general formula (9) is condensed with a compound represented by a general formula (13) to form a compound represented by a general formula (14) (Step 10). The compound thus obtained is allowed to react in the same manner as in Step 6 and Step 7 of Preparation Process 2, whereby a compound repre-

5 sented by a general formula (16) can be obtained. Subsequently, the compound (16) can be converted into a compound (1-3) according to the present invention in the same manner as in Step 8 and Step 1 of Preparation Process 2. When A¹ in the compound represented by the general formula (16) is a single bond, the compound is subjected to a Mitsunobu reaction in the same manner as in Step 9 of Preparation Process 2, whereby a compound (1-4) according to the present invention can be obtained. Step 10 will hereinafter be described in detail.

Step 10:

10 [0044] The compound (13), which is a starting material, can be purchased as a commercially available reagent or prepared in accordance with a known method [for example, a method described in Organic Synthesis Collect, Volume II, 387, Japanese Patent Application Laid-Open No. 136391/1994, or the like]. This compound is condensed with the compound represented by the general formula (9) in the presence of a proper base or catalyst, whereby the compound (a mixture of E:Z) of the general formula (14) can be prepared. Examples of the base used in the reaction include sodium hydride, potassium t-butoxide and pyridine. When the catalyst is used, piperidine and acetic acid, piperidinium acetate, piperidinium benzoate, or the like may be used. No particular limitation is imposed on a solvent used so far as it does not affect the reaction. Examples of the solvent used include ethers such as tetrahydrofuran and dioxane; hydrocarbons such as benzene and toluene; amides such as dimethylformamide, dimethylacetamide and N-methyl- α -pyrrolidone; and sulfoxides such as dimethyl sulfoxide.

<Preparation Process 4> Case of $R^1 = H$ in the general formula (1):



wherein W, A, Y¹, R², R³, X¹ and A² have the same meanings as defined above, R⁸ is a lower alkyl group, and X² is O or NH.

[0045] More specifically, a compound represented by a general formula (17) is converted into a compound (1-5)

according to the present invention by an ordinary alkylating method (Step 11). Subsequently, this compound is hydrolyzed or reacted with any of various amines, whereby a compound (1-6) according to the present invention can be prepared (Step 12). Alternatively, the compound (5) and a compound (18) are successively treated in the same manner as in Step 10 of Preparation Process 3 and Step 7 of Preparation Process 2, whereby the compound (1-5) according to the present invention can also be obtained. The individual steps will hereinafter be described.

Step 11:

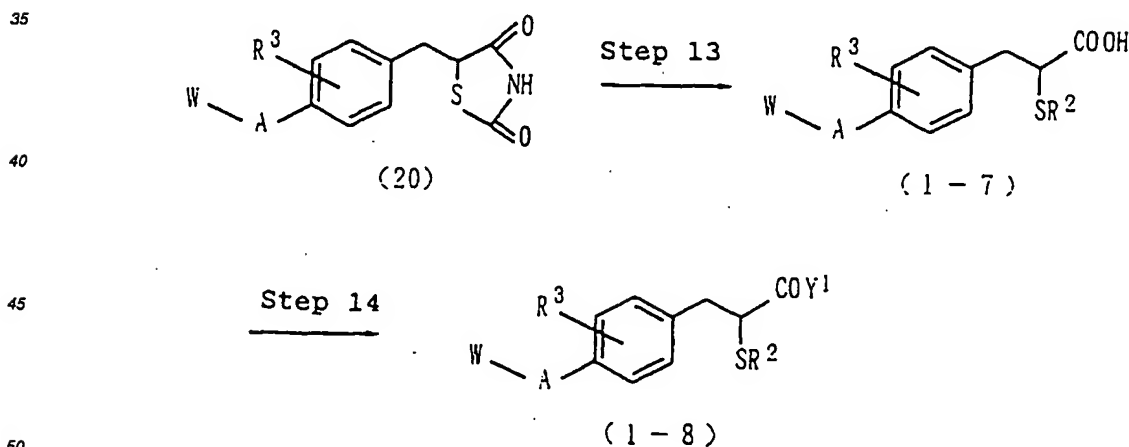
[0046] The compound represented by the general formula (17), which is a starting material, can be synthesized in accordance with a known method [for example, a method described in Organic Synthesis Collect, Volume III, 586 (1955); Journal of Chemical Society, 1808 (1951); Synthesis, 793 (1992); Japanese Patent Application Laid-Open No. 325263/1996; or the like]. This compound or a salt thereof is reacted with a halide (iodide, bromide or chloride), whereby the compound (1-5) according to the present invention can be obtained. This reaction is carried out in the presence of a base in a proper solvent. Examples of the solvent used include dimethylformamide, dimethyl sulfoxide, methanol, ethanol, ethoxyethanol, tetrahydrofuran, dioxane and acetonitrile. Examples of the base used include triethylamine, N,N-diisopropylethylamine, pyridine, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium hydrogencarbonate, sodium hydride and potassium hydride. The reaction is performed at room temperature or under heating with stirring.

Step 12:

[0047] The compound (1-5) according to the present invention is hydrolyzed in the presence of proper solvent and base, whereby the compound (1-6) according to the present invention can be obtained as its corresponding carboxylic acid. Alternatively, the compound (1-5) according to the present invention is reacted with any of various amines in the presence or absence of a solvent, or the above carboxylic acid is converted into an active derivative (for example, an acid halide or mixed acid anhydride) and then reacted with any of various amines, whereby the compound (1-6) according to the present invention can be prepared. With respect to the solvent and base used in the hydrolysis, the same conditions as those in Step 6 of Preparation Process 1 may be used.

<Preparation Process 5>

Case of $R^1 = H$ and $X = S$ in the general formula (1):



wherein W, A, R^2 , R^3 and Y^1 have the same meaning as defined above.

[0048] More specifically, a compound represented by a general formula (20) is hydrolyzed under basic conditions and then reacted with its corresponding halide, whereby a compound (1-7) according to the present invention (Step 13). This compound is further converted into an active carboxylic acid derivative and then reacted with any of various amines and alcohols, whereby a compound (1-8) according to the present invention can be prepared (Step 14). The individual steps will hereinafter be described.

Step 13:

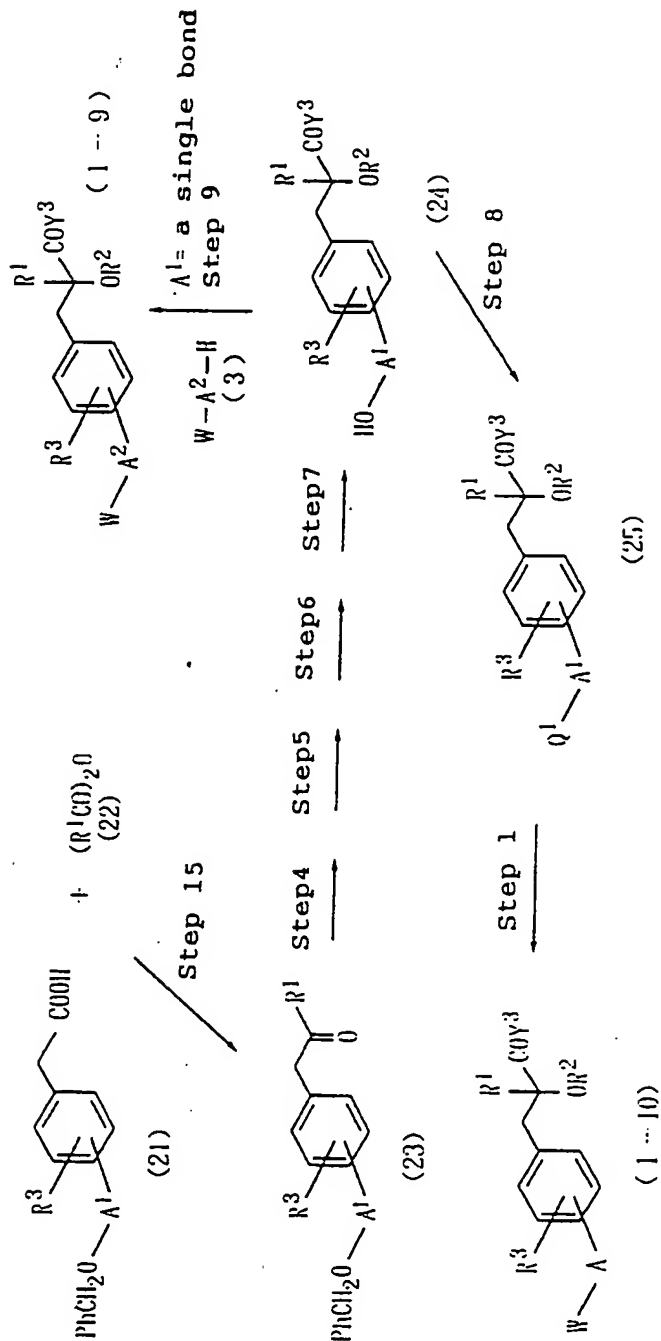
[0049] The compound represented by the general formula (20) (EP 0787727-A1), which is a starting material, is hydrolyzed under basic conditions and then reacted with its corresponding halide, whereby the compound (1-7) according to the present invention can be prepared. Specifically, after the compound of the general formula (20) is gently heated to reflux for 0.5 to 1 hour in a 15% aqueous solution of sodium hydroxide, a methanol solution of the corresponding halide (iodide, bromide or chloride) is added at room temperature, and the mixture is stirred for about 1 to 3 hours, whereby the compound (1-7) according to the present invention can be obtained.

Step 14:

[0050] The carboxylic acid, which is the compound (1-7) according to the present invention, is converted into an active derivative (for example, an acid halide or mixed acid anhydride) and then reacted with any of various amines and alcohols, or the compound (1-7) according to the present invention is reacted with any of various amines and alcohols in the presence of a proper condensation agent, whereby the compound (1-8) according to the present invention can be prepared.

[0051] Examples of the condensation agent used include carbonyldiimidazole, 1-hydroxy-2(1H)-pyridone, N-hydroxysuccinimide, diphenylphosphorylazide, N,N-dicyclohexylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride. The reaction is carried out in the presence of a proper base, for example, an organic base such as triethylamine or pyridine, according to the kind of the condensation agent used.

<Preparation Process 6> Case of $X = O$ and $R^1 = \text{alkyl}$ in the general formula (1):



wherein $W, A, A^1, A^2, Y^3, R^1, R^2, R^3$ and Q^1 have the same meanings as defined above.

[0052] More specifically, after a compound (21) is reacted with a compound (22) to form a compound (23) (Step 15), exactly the same reactions as in Steps 4, 5, 6 and 7 of Preparation Process 2 are conducted, whereby a compound (24)

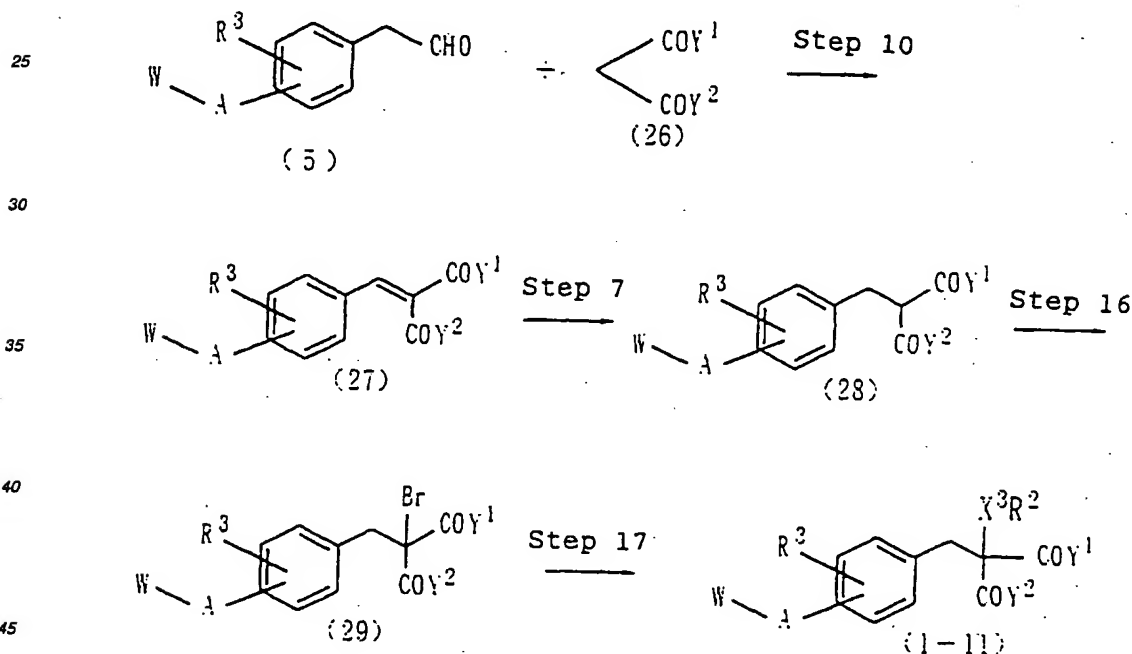
can be prepared. After the terminal hydroxy group of the resultant compound (24) is converted into a leaving group (Q^1) in the same manner as in Step 8 of Preparation Process 2, the resultant compound is allowed to react in the same manner as in Step 1 of Preparation Process 2, whereby a compound (1-10) according to the present invention can be prepared. When A^1 in the compound represented by the general formula (24) is a single bond, the compound is subjected to the Mitsunobu reaction with a compound represented by the general formula (3) in the same manner as in Step 9 of Preparation Process 2, whereby a compound (1-9) according to the present invention can be prepared. Step 15 will hereinafter be described in detail.

Step 15:

[0053] The compound (21), which is a starting material, can be purchased as a commercially available reagent or prepared from the compound (9) in accordance with a known method [for example, a method described in Journal of Organic Chemistry, 21, 1149 (1956); Angewandte Chemie, 80, 364 (1968); or the like]. This compound (21) is heated and stirred in the presence of an acid anhydride (22) and a base in accordance with a method described in literature [for example, Journal of American Chemical Society, 72, 1988 (1950); Journal of American Chemical Society, 73, 4911 (1951); Journal of Medicinal Chemistry, 39, 3897 (1996); or the like], whereby the compound (23) can be prepared. Examples of the base used include pyridine, sodium acetate and potassium acetate.

<Preparation Process 7>

Case of $R^1 =$ group COY^2 in the general formula (1):



wherein R^2 , R^3 , Y^1 , Y^2 , A and W have the same meaning as defined above, and X^3 is O, S or NH.

[0054] More specifically, a compound represented by the general formula (5) is condensed with a malonic acid derivative represented by a general formula (26) in the same manner as in Step 10 of Preparation Process 4, thereby obtaining a compound represented by a general formula (27). The compound thus obtained is reduced in the same manner as in Step 7 of Preparation Process 2 to convert it into a compound represented by a general formula (28), and the compound (28) is then subjected to a brominating reaction, whereby a compound represented by a general formula (29) can be prepared (Step 16). Finally, the compound (29) is reacted with any of various nucleophilic reagents, whereby a compound (1-11) according to the present invention can be prepared (Step 17). Steps 16 and 17 will hereinafter be described in detail.

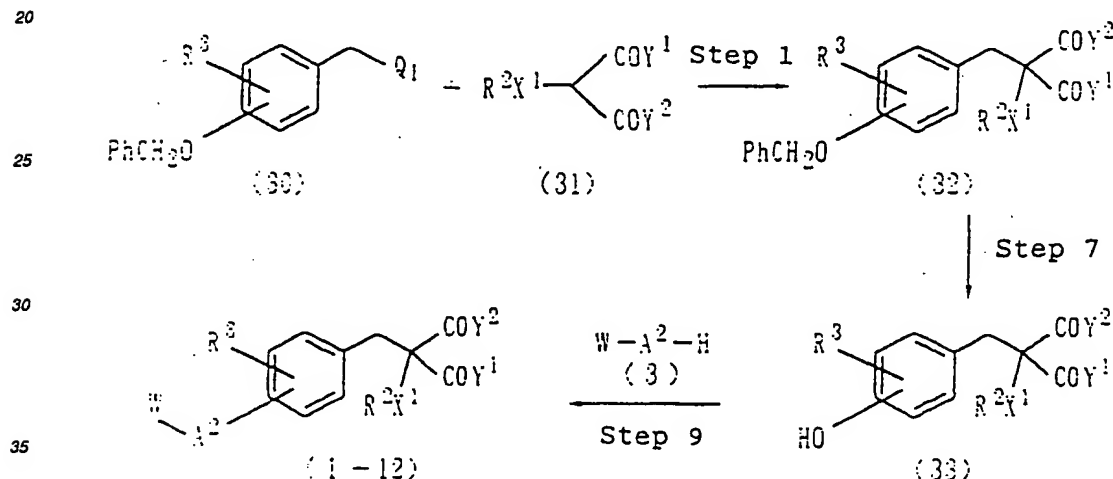
Step 16:

[0055] The compound represented by the general formula (28) is reacted with bromine in the presence of a proper solvent in accordance with a known method [for example, a method described in Organic Synthesis Collect Volume III, 705 (1955); Organic Synthesis Collect Volume I, 245 (1945); Tetrahedron Letters, 24, 163 (1983); or the like], whereby the compound represented by the general formula (29) can be prepared. Examples of the solvent used include acetic acid, diethyl ether, dioxane and carbon tetrachloride.

Step 17:

[0056] The compound represented by the general formula (29) is reacted with any of various alcohols, amines and thiols in the presence of proper solvent and base, whereby the compound (1-11) according to the present invention can be prepared. No particular limitation is imposed on the solvent used so far as it does not affect the reaction. Examples thereof include various kinds of alcohols, dioxane, tetrahydrofuran, dimethylformamide and dimethyl sulfoxide. Examples of the base used include sodium hydroxide, potassium hydroxide, potassium carbonate, sodium hydrogen carbonate, sodium hydride, triethylamine and pyridine.

<Preparation Process 8>



wherein R^2 , R^3 , X^1 , Y^1 , Y^2 , A^2 , Q^1 and W have the same meanings as defined above.

[0057] More specifically, a compound represented by a general formula (30) is reacted with a compound represented by a general formula (31) in the same manner as in Step 1 of Preparation Process 1, thereby obtaining a compound (32). The compound thus obtained is then catalytically reduced in the same manner as in Step 7 of Preparation Process 2 to obtain a compound (33). Finally, the compound (33) is reacted with the compound (3), whereby a compound (1-12) according to the present invention can be prepared.

[0058] The compound (1) according to the present invention obtained by each of the above-described preparation processes can be isolated in the form of crystals or a liquid, as needed, by the conventional means for isolation and purification, for example, recrystallization, distillation and/or chromatography. The compound may also be converted into a salt or solvate as needed.

[0059] The compounds (1) according to the present invention are excellent in the effect of lowering blood glucose and lipid and hence useful as medicines for preventing or treating diabetes mellitus, hyperlipemia, obesity and the like.

[0060] The medicine according to the present invention is prepared by formulating an effective amount of the compound (1) or the salt thereof as an active ingredient in suitable combination with pharmaceutically acceptable, known carriers, for example, excipients, binders, disintegrators, lubricants, dissolution aids, suspending agents and the like according to pharmacological effects intended, administration object, administration end, administration form, etc. Examples of administration forms include oral administrations by tablets, capsules, granules, powder, syrup, etc., and parenteral administrations by injections, ophthalmic solutions suppositories, etc. In the medicine according to the present invention, the dose of the compound (1) varies according to the condition, age and weight of a patient to be administered, and the administration method thereof. However, the compound (1) may be generally administered in a

dose of 0.1 to 1,000 mg per day for an adult.

[0061] The compounds (1) according to the present invention may also be used as veterinary medicines for other mammals than the human.

[0062] The present invention will hereinafter be described more specifically by the following Preparation Examples, Examples and Test Example. However, these examples are intended to illustrate the present invention and by no means limit the present invention.

Preparation Example 1:

10 Preparation of 4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]benzaldehyde (Compound 5):

[0063] After dimethylformamide (100 ml) was added to a mixture of 1-phthalazinone (1.46 g), 4-[2-(methanesulfonyloxy)ethoxy]benzaldehyde (2.44 g) and potassium carbonate (2.07 g), and the mixture was heated and stirred for 4 hours at 85 to 90°C on an oil bath, the reaction mixture was poured into ice water and extracted with ethyl acetate. After the resultant extract was washed with water and then with brine, it was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel. A chloroform eluate was crystallized from ether to obtain the title compound (2.17 g, yield: 73.8%) as colorless crystals.

20 ¹H-NMR (CDCl₃, δ):
4.52(2H,t), 4.68(2H,t), 7.00(2H,d), 7.71-7.86(5H,m), 8.19(1H,s), 8.44(1H,dd), 9.86(1H,s).

Preparation Example 2:

25 Preparation of 4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]benzaldehyde (Compound 5):

[0064] Dimethyl sulfoxide (100 ml) was added to 2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethanol (11.6 g) and p-fluorobenzaldehyde (11.2 g) to prepare a solution. After sodium hydride (3.6 g; 60% assay) was added portionwise to the solution under ice cooling, the mixture was stirred at room temperature for 2.5 hours. Thereafter, the reaction mixture was poured into ice water, and the precipitate was collected by filtration, washed with water and dried under reduced pressure. After ether was added to the thus-obtained crude crystals, and the resultant mixture was heated and stirred, the mixture was cooled down to room temperature. The preprecipitate was collected by filtration and dried to obtain the title compound (15.4 g, yield: 86.3%) as colorless crystals.

35 ¹H-NMR (CDCl₃, δ):
3.99(2H,t), 4.36(2H,t), 5.37(2H,s), 6.97-7.01(3H,m), 7.12(1H,brt), 7.45(1H,ddd), 7.84(2H,d), 7.95(1H,ddd), 9.89(1H,s).

Preparation Example 3:

40 Preparation of 2-[2-[4-(2-methoxyvinyl)phenoxy]ethyl]-1,2-dihydro-1-phthaladinone (Compound 6):

[0065] (Methoxymethyl)triphenylphosphonium chloride (13.71 g, 40 mmol) and diisopropylamine (4.22 ml, 30 mmol) were suspended in anhydrous tetrahydrofuran (100 ml). A 1.58 M hexane solution (19 ml, 30 mmol) of n-butyllithium was added to the suspension at -10°C, and the mixture was stirred for 1 hour. A solution of 4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]benzaldehyde (Compound 5) (5.88 g, 20 mmol) in tetrahydrofuran (40 ml) was then added dropwise to the mixture at the same temperature, and the resultant mixture was stirred for 2 hours at -10°C to room temperature. After completion of the reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. The resultant extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (a mixture of E/Z) (6.5 g, yield: 99%) as pale yellow crystals.

55 ¹H-NMR (CDCl₃, δ):
3.64(1.5H,s), 3.73(1.5H,s), 4.34-4.70(4H,m), 5.10(0.5H,d), 5.75(0.5H,d), 6.05(0.5H,d), 6.80-7.51(4.5H,m), 7.68-7.84(3H,m), 8.17(1H,s), 8.39-8.48(1H,m).

Preparation Example 4:

Preparation of 2-[2-[4-(2,2-diethoxyethyl)phenoxy]ethyl]-1,2-dihydro-1-phthaladinon (Compound 7):

[0066] Ethanol (200 ml) was added to 2-[2-[4-(2-methoxyvinyl)phenoxy]ethyl]-1,2-dihydro-1-phthaladinone (Compound 6) (6.44g, 20 mmol) and p-toluenesulfonic acid hydrate (0.38 g, 2 mmol), and the mixture was heated under reflux for 6 hours. After completion of the reaction, the solvent was removed, and ethyl acetate was added to the resultant residue. After the resultant mixture was washed successively with a 5% aqueous solution of sodium hydrogencarbonate and brine and dried over anhydrous magnesium sulfate, the solvent was removed to obtain the title compound (7.2 g, yield: 94.2%) as a pale yellow oil.

¹H-NMR (CDCl₃, δ):

1.15(6H,t), 2.85(2H,d), 3.34-3.75(4H,m), 4.32-4.72(5H,m), 6.84(2H,d), 7.10(2H,d), 7.69-7.85(3H,m), 8.18(1H,s), 8.34-8.50(1H,m).

Preparation Example 5:

Preparation of 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propionitrile (Compound 8):

[0067] 2-[2-[4-(2,2-Diethoxyethyl)phenoxy]ethyl]-1,2-dihydro-1-phthaladinone (Compound 7) (7.2 g, 18.8 mmol) was dissolved in dichloromethane (100 ml). Trimethylsilyl nitrile (7.52 ml, 56.4 mmol) and boron trifluoride etherate (0.58 ml, 4.7 mmol) were successively added to the solution, and the mixture was stirred for 1 hour. After completion of the reaction, dichloromethane was added to the reaction mixture. After the resultant mixture was washed with a 5% aqueous solution of sodium hydrogencarbonate and water and dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (6.0 g, yield: 88.0%) as colorless crystals.

¹H-NMR (CDCl₃, δ):

1.22(3H,t), 3.05(2H,d), 3.30-4.00(2H,m), 4.19(1H,t), 4.40-4.70(4H,m), 6.85(2H,d), 7.15(2H,d), 7.68-7.84(3H,m), 8.17(1H,s), 8.39-8.50(1H,m).

Preparation Example 6:

Preparation of 2-ethoxy-3-[4-(2-hydroxyethyl)phenyl]propanamide (Compound 11):

[0068] 2-Ethoxy-3-[4-(2-benzyloxyethyl)phenyl]propanamide (Compound 10) (13.04 g) was dissolved in ethanol (150 ml) and acetic acid (30 ml). To the solution, was added 10% palladium on charcoal (8 g), followed by hydrogenation at room temperature for 4 hours. After completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (CHCl₃:MeOH = 100:2) to obtain the title compound (8.38 g, yield: 88.6%) as a colorless oil.

¹H-NMR (CDCl₃, δ):

1.14(3H,t), 2.71-4.04(10H,m), 6.18(1H,brs), 6.52(2H,brs), 7.08-7.32(4H,m).

Preparation Example 7:

Preparation of 2-ethoxy-3-[4-[2-(methanesulfonyloxy)ethyl]phenyl]propanamide (Compound 12):

[0069] 2-Ethoxy-3-[4-(2-hydroxyethyl)phenyl]propanamide (Compound 11) (8.38 g, 35.3 mmol) and triethylamine (4.29 g, 42.4 mmol) were dissolved in methylene chloride (80 ml). Methanesulfonyl chloride (4.85 g, 42.4 mmol) was added dropwise to the solution under ice cooling, and the resultant mixture was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and brine in that order, and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure to obtain the title compound (8.44 g, yield: 75.8%) as colorless crystals.

¹H-NMR (CDCl₃, δ):

1.14(3H,t), 2.78-3.64(9H,m), 3.81-4.05(1H,m), 4.41(2H,t), 5.74(1H,brs), 6.48(1H,brs), 7.08-7.23(4H,m).

Preparation Example 8:

Preparation of 3-[4-(benzyloxy)phenyl]-2-methoxy-2-propenenitrile (Compound 14):

- 5 [0070] 4-Benzyloxybenzaldehyde (2.12 g, 10 mmol) and methoxyacetonitrile (748 mg, 10 mmol) were dissolved in dimethylformamide (30 ml). Sodium hydride (60% assay; 480 mg, 12 mmol) was added to the solution at room temperature, and the resultant mixture was heated and stirred for 1 hour at 110°C on an oil bath. After completion of the reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate. After the resultant extract was washed with brine and dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure.
- 10 The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to obtain the title compound (a mixture of E/Z; 1.58 g, yield: 59.7%) as colorless syrup.

- ¹H-NMR (CDCl₃, δ):
 3.76(1.5H,s), 3.90(1.5H,s), 5.09(2H,s), 6.14(0.5H,s), 6.53(0.5H,s), 6.95(1H,d), 6.98(1H,d), 7.10-
 15 7.40(5H,m), 7.51(1H,d), 7.58(1H,d).

Example 1:

- Preparation of 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide [Invention Compound (1A)]:
- 20 (1A):

- [0071] 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propionitrile (Compound 8) (6.0 g, 16.5 mmol) was dissolved in ethanol (200 ml), and a 6N aqueous solution (8.25 ml, 49.5 mmol) of sodium hydroxide was added to the solution. The resultant mixture was heated under reflux for 1.5 hours. After completion of the reaction, water was added to the reaction mixture to conduct extraction with ethyl acetate. The resultant extract was washed with
 25 brine and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) and recrystallized from ethyl acetate to obtain Invention Compound (1A) (3.3 g, yield: 52.5%) as colorless crystals.

- 30 Example 2:

[0072] Invention Compounds (1D), (1F), (1H), (1J), (1K), (1N), (1AB), (1AC), (1BG), (1BU) and (1BV) were prepared in the same manner as in Example 1.

- 35 Example 3:

Preparation of 2-ethoxy-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethyl]phenyl]propanamide [Invention Compound (1Q)]:

- 40 [0073] 4-Quinazoline (500 mg, 3.42 mmol), 2-ethoxy-3-[4-[2-(methanesulfonyloxy)ethyl]phenyl]propanamide (Compound 12) (1.13 g, 3.42 mmol) and potassium carbonate (1.42 g, 10.3 mmol) were dissolved in dimethylformamide (20 ml), and the resultant solution was heated and stirred at 80°C for 2 hours. After cooling the reaction mixture, water was added to the reaction mixture to conduct extraction with ethyl acetate. The resultant extract was washed with water and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The precipitate was
 45 collected by filtration and washed with ether. The crude crystals thus obtained were recrystallized from ethanol to obtain Invention Compound (1Q) (1.11 g, yield: 87.6%).

Example 4:

- 50 [0074] Invention Compounds (1E), (1G), (1I), (1S), (1T), (1U), (1V), (1W), (1X), (1Y), (1AF), (1AI) and (1BR) were prepared in the same manner as in Example 3.

Example 5:

- 55 Preparation of 2-methoxy-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanamide [Invention Compound (1P)]:

[0075] 2-(4-Oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethanol (794 mg, 4.11 mmol), 2-methoxy-3-(4-hydroxyphenyl)-

propanamide (802 mg, 4.11 mmol) and triphenylphosphine (1.13 g, 4.31 mmol) were dissolved in tetrahydrofuran (20 ml), and a 40% toluene solution of diethyl azodicarboxylate (1.88 g, 4.31 mmol) was added dropwise to the solution under ice cooling. The resultant mixture was stirred overnight at room temperature. After completion of the reaction, the solvent was removed under reduced pressure. Ether was added to the residue, and the resultant mixture was washed with a 10% aqueous solution of sodium hydroxide and brine. An organic layer was dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain Invention Compound (1P) (976 mg, yield: 64.1%) as colorless crystals.

10 Example 6:

[0076] Invention Compounds (1R), (1AH), (1AJ), (1AK), (1AL), (1AM), (1AS), (1AT), (1AV), (1AY), (1AZ) and (1BE) were prepared in the same manner as in Example 5.

15 Example 7:

Preparation of ethyl 2-ethylamino-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propionate [Invention Compound (1L)]:

20 [0077] Ethyl 2-amino-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propionate hydrochloride (1.05 g, 2.5 mmol) was dissolved in ethanol (10 ml), and ethyl iodide (390 mg, 2.5 mmol) and diisopropylethylamine (323 mg, 2.5 mmol) were added dropwise to the solution. The resultant mixture was stirred for 2 days at 60°C [during which additional ethyl iodide and diisopropylethylamine (each, 5 mmol) were added]. After completion of the reaction, the solvent was removed, and ethyl acetate was added to the residue. The resultant mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure, and the resultant residue was purified by column chromatography on silica gel to obtain Invention Compound (1L) (627 mg, yield: 60.8%) as a colorless oil.

Example 8:

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Preparation of 2-ethylamino-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propionic acid [Invention Compound (1M)]:

35 [0078] A 1N aqueous solution (5 ml) of sodium hydroxide was added to a solution of ethyl 2-ethylamino-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propionate (627 mg) in ethanol (8 ml), and the resultant mixture was stirred overnight at 60°C. After the completion of a reaction was confirmed by using TLC, the reaction mixture was concentrated under reduced pressure. Water was added to the residue, and the resultant mixture was neutralized with 3% hydrochloric acid. The precipitate was then collected by filtration, washed with water and then dried to obtain Invention Compound (1M) (640 mg, quantitative) in the form of the hydrochloride as colorless crystals.

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Example 9:

[0079] Invention Compounds (1BA), (1BB) and (1BF) were prepared in the same manner as in Example 8.

45 Example 10:

Preparation of 2-ethylthio-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propanoic acid [Invention Compound (1O)]:

50 [0080] A 15% aqueous solution (60 ml) of sodium hydroxide was added to 5-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]benzyl}-2,4-thiazolidinedione (3.0 g). After the resultant mixture was gently heated to reflux for 30 minutes, methanol (60 ml) was then added to the mixture at room temperature, and a methanol solution of ethyl iodide (5.3 g) was then added dropwise, followed by stirring for 1.5 hours. Thereafter, the reaction mixture was poured into ice water, acidified with hydrochloric acid and extracted with ethyl acetate. The resultant extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel (chloroform:methanol = 50:1) and crystallized from hexane-ethyl acetate to obtain Invention Compound (1O) (600 mg, yield: 19.9%) as colorless crystals.

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Example 11:

Preparation of 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoic acid [Invention Compound (1B)]:

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[0081] 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide [Invention Compound (1A)] (12.55 g, 32.9 mmol) was dissolved in dioxane (148 ml), and 2N hydrochloric acid (16.5 ml, 32.9 mmol) and a catalytic amount of TiCl_4 were added to the solution, followed by stirring at 110°C for 6 hours. After completion of the reaction, the solvent was removed, and chloroform was added to the residue. The precipitate was removed by filtration, and the filtrate was dried over anhydrous magnesium sulfate. The solvent was then removed, and the resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:3) and recrystallized from ethyl acetate to obtain Invention Compound (1B) (5.23 g, yield: 41.8%) as colorless crystals.

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Example 12:

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[0082] Invention Compounds (1AE), (1BC), (1BD), (1BJ), (1BK), (1BL) and (1BS) were prepared in the same manner as in Example 11.

Example 13:

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Preparation of ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoate [Invention Compound (1C)]:

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[0083] 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide [Invention Compound (1A)] (1.0 g, 2.62 mmol) was dissolved in ethanol (30 ml), and 1N hydrochloric acid (2.6 ml, 2.6 mmol) and a catalytic amount of TiCl_4 were added to the solution, followed by refluxing for 5 hours. After completion of the reaction, the solvent was removed, and chloroform was added to the residue. The precipitate was removed by filtration, and the filtrate was dried over anhydrous magnesium sulfate. The resultant residue was then purified by column chromatography on silica gel (hexane:ethyl acetate = 2:3) to obtain Invention Compound (1C) (0.2 g, yield: 20.0%) as a colorless oil.

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Example 14:

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[0084] Invention Compounds (1AN), (1AO), (1AP), (1AQ), (1AU), (1AW), (1AX) and (1BO) were prepared in the same manner as in Example 13.

Example 15:

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Preparation of 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanchydroxamic acid [Invention Compound (1AA)]:

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[0085] 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoic acid [Invention Compound (1B)] (500 mg, 1.31 mmol) was dissolved in dimethylformamide (10 ml), and carbonyldiimidazole (233 mg, 1.44 mmol) was added to the solution. After the resultant mixture was stirred at room temperature for 1 hour, hydroxylamine hydrochloride (200 mg, 2.88 mmol) was added, and the mixture was stirred at the same temperature for 12 hours. After completion of the reaction, water was added to the reaction mixture to conduct extraction with ethyl acetate. The resultant extract was washed with water and then with brine, and dried over anhydrous magnesium sulfate. The solvent was then removed, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 3:2 to 4:1) and recrystallized from a mixed solvent of ethyl acetate and ether to obtain Invention Compound (1AA) (150 mg, yield: 28.8%) as colorless crystals.

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Example 16:

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[0086] Invention Compounds (1Z), (1AD), (1AG), (1BH) and (1BP) were prepared in the same manner as in Example 15.

Example 17:

Preparation of ethyl 2-ethoxy-3-{4-[2-(4-methyl-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl}propanoate [Invention Compound (1BI)]:

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[0087] Ethyl 2-ethoxy-3-{4-[2-(4-methyl-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl}propenoate (4.96 g, 11.75 mmol) was dissolved in ethyl acetate (60 ml), and 10% palladium on carbon (600 mg) was added to conduct catalytic reduction for 10 hours. After completion of the reaction, the catalyst was removed by filtration, and the filtrate was concentrated. The resultant residue was purified by column chromatography on silica gel to obtain Invention Compound (1BI) (4.54 g, yield: 91.2%) as colorless crystals.

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Example 18:

[0088] Invention Compounds (1AR), (1BM), (1BN), (1BQ), (1BT) and (1BW) were prepared in the same manner as in Example 17.

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[0089] The structures and physical data of the compounds obtained in the above-described Examples are shown in the following tables. W, A, R¹, R², R³, X and Y¹ in the tables mean the respective symbols in the general formula (1). The position of substitution (abbreviated as "PS" in the tables) indicates the position of W-A- substituted on a benzene ring.

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Table 1

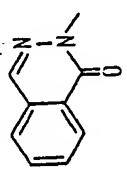
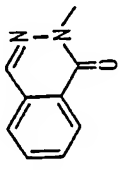
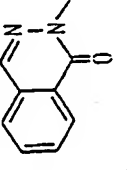
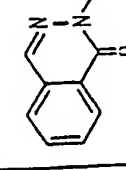
No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDCl ₃ , δ)
1A		-CH ₂ -CH ₂ -O-	4	H	Et	H	O	NH ₂	128-129	1.11 (3H, t), 2.85 (1H, dd), 3.05 (1H, dd), 3.38-3.52 (2H, m), 3.85 (1H, dd), 4.40 (2H, t), 4.64 (2H, t), 5.48 (1H, br), 6.42 (1H, br), 6.83 (2H, d), 7.12 (2H, d), 7.69-7.84 (3H, m), 8.19 (1H, s), 8.45 (1H, dd)
1B		-CH ₂ -CH ₂ -O-	4	H	Et	H	O	OH	113-115	1.15 (3H, t), 2.91 (1H, dd), 3.05 (1H, dd), 3.38-3.61 (2H, m), 4.02 (1H, dd), 4.40 (2H, t), 4.64 (2H, t), 6.85 (2H, d), 7.13 (2H, d), 7.69-7.84 (3H, m), 8.19 (1H, s), 8.43-8.45 (1H, m)
1C		-CH ₂ -CH ₂ -O-	4	H	Et	H	O	OEt	oil	1.14 (3H, t), 1.21 (3H, t), 2.91-2.93 (2H, m), 3.29-3.36 (1H, m), 3.54-3.62 (1H, m), 3.93 (1H, dd), 4.14-4.18 (2H, m), 4.40 (2H, t), 4.64 (2H, t), 6.84 (2H, d), 7.12 (2H, d), 7.69-7.84 (3H, m), 8.18 (1H, s), 8.43-8.45 (1H, m)
1D		-CH ₂ -CH ₂ -O-	4	H	Et	3-OMe	O	NH ₂	137-140	1.12 (3H, t), 2.82 (1H, dd), 3.07 (1H, dd), 3.37-3.54 (2H, m), 3.77 (3H, s), 3.87 (1H, dd), 4.45 (2H, t), 4.67 (2H, t), 5.50 (1H, br), 6.45 (1H, br), 6.74-6.78 (2H, m), 6.90 (1H, d), 7.69-7.84 (3H, m), 8.19 (1H, s), 8.43-8.45 (1H, m)

Table 2

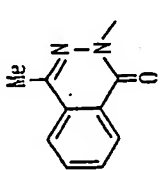
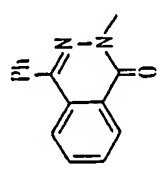
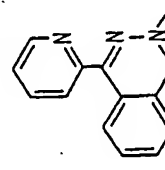
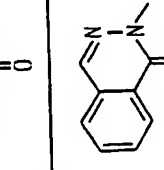

No	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDC l ₃ , δ)
IE		-CH ₂ -CH ₂ -O-	4	II	Et	II	0	NH ₂	141-145	1. 12(3H, l), 2. 60(3H, s), 2. 85(1H, dd), 3. 06(1H, dd), 3. 36-3. 53(2H, m), 3. 86(1H, dd), 4. 39(2H, l), 4. 60(2H, l), 5. 42(1H, br), 6. 42(1H, br), 6. 84(2H, d), 7. 12(2H, d), 7. 74-7. 84(3H, m), 8. 46-8. 48(1H, m)
IF		-CH ₂ -CH ₂ -O-	4	II	Et	II	0	NH ₂	87-88	1. 11(3H, l), 2. 83(1H, dd), 3. 05(1H, dd), 3. 32-3. 52(2H, m), 3. 85(1H, dd), 4. 44(2H, l), 4. 71(2H, l), 5. 59(1H, brs), 6. 42(1H, brs), 6. 85(2H, d), 7. 12(2H, d), 7. 52-7. 59(5H, m), 7. 72-7. 81(3H, m), 8. 53-8. 55(1H, m)
IG		-CH ₂ -CH ₂ -O-	4	II	Et	II	0	NH ₂	138-140	1. 11(3H, l), 2. 83(1H, dd), 3. 05(1H, dd), 3. 35-3. 52(2H, m), 3. 85(1H, dd), 4. 45(2H, l), 4. 73(2H, l), 5. 51(1H, br), 6. 41(1H, br), 6. 84(2H, d), 7. 12(2H, d), 7. 40-7. 43(1H, m), 7. 76-7. 90(4H, m), 8. 42-8. 45(1H, m), 8. 50-8. 53(1H, m), 8. 75-8. 77(1H, m)
IIH		 -CH ₂ -CH ₂ -O-	4	II	Et	II	0	NH ₂	104-106	1. 14(3H, l), 2. 86(1H, dd), 3. 08(1H, dd), 3. 40-3. 55(2H, m), 3. 80(1H, d), 3. 89(1H, dd), 4. 05-4. 13(2H, m), 4. 47-4. 62(3H, m), 5. 40(1H, br), 6. 43(1H, br), 6. 85(2H, d), 7. 15(2H, d), 7. 72-7. 74(1H, m), 7. 79-7. 87(2H, m), 8. 21(1H, s), 8. 44(1H, d)

Table 3

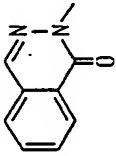
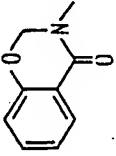
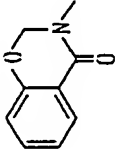
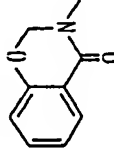
Nit	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDCl ₃ , δ)
II		-CH ₂ -CH ₂ -	4	H	Et	H	0	NH ₂	146-149	1.13(3H, t), 2.86(1H, dd), 3.09-3.15(3H, m), 3.40-3.53(2H, m), 3.90(1H, dd), 4.43-4.47(2H, m), 5.53(1H, br), 6.44(1H, br), 7.18(2H, d), 7.20(2H, d), 7.68-7.83(3H, m), 8.16(1H, s), 8.42(1H, dd)
IJ		-CH ₂ -CH ₂ -O-	4	H	Et	H	0	NH ₂	101-102	1.13(3H, t), 2.86(1H, dd), 3.07(1H, dd), 3.38-3.54(2H, m), 3.87(1H, dd), 3.95(2H, t), 4.18(2H, t), 5.3 (1H, brs), 5.37(2H, s), 6.40(1H, brs), 6.79(2H, d), 6.97(1H, dd), 7.09-7.14(1H, m), 7.15(2H, d), 7.42-7.46(1H, m), 7.95(1H, dd)
IK		-CH ₂ -CH ₂ -O-	4	H	Et	H	0	OH	98-99	1.16(3H, t), 2.94(1H, dd), 3.06(1H, dd), 3.38-3.46(1H, m), 3.55-3.63(1H, m), 3.95(2H, t), 4.02(1H, dd), 4.17(2H, t), 5.37(2H, s), 6.80(2H, d), 6.97(1H, d), 7.10(1H, dt), 7.42-7.46(1H, m), 7.95(1H, dd)
IL		-CH ₂ -CH ₂ -O-	4	H	Et	H	NH	OH	Oil	1.06(3H, t), 1.15(3H, t), 2.48-2.58(1H, m), 2.60-2.67(1H, m), 2.82-2.93(2H, m), 3.46(1H, t), 3.94(2H, t), 4.09(2H, q), 4.17(2H, t), 5.36(2H, s), 6.79(2H, d), 6.96(1H, d), 7.07-7.12(3H, m), 7.43(1H, dt), 7.95(1H, dd)

Table 4

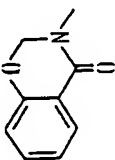
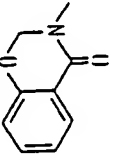
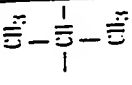
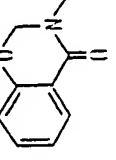
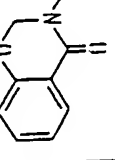
Mat	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m.p. (°C)	NMR (CDCl ₃ , δ)
IN		-CH ₂ -CH ₂ -O-	-I	II	Et	II	NH	III	228-229 (HCl salt)	0.99 (3H, t), 2.38-2.49 (1H, m), 2.50-2.55 (1H, m), 2.72-2.83 (2H, m), 3.26 (1H, t), 3.72 (2H, t), 4.03 (2H, t), 4.81 (2H, s), 6.74-6.77 (3H, m), 6.97 (1H, t), 7.09 (2H, d), 7.30 (1H, dt), 7.66 (1H, dd), (D ₂ O+NaOD) (HCl salt)
IN		-CH ₂ -CH ₂ -O-	-I	II		II	O	NH ₂	82-83	0.95 (3H, d), 1.11 (3H, d), 2.80 (1H, dd), 3.05 (1H, dd), 3.45 (1H, ddd), 3.92 (1H, dd), 3.95 (2H, t), 4.18 (2H, t), 5.37 (2H, s), 5.43 (1H, br), 6.49 (1H, br), 6.79 (2H, d), 6.97 (1H, d), 7.11 (1H, d), 7.16 (2H, d), 7.42-7.46 (1H, m), 7.95 (1H, dd)
IO		-CH ₂ -CH ₂ -O-	-I	II	Et	II	S	III	71-72	1.22 (3H, t), 2.61-2.68 (2H, m), 2.89 (1H, dd), 3.13 (1H, dd), 3.47 (1H, dd), 3.94 (2H, t), 4.14 (2H, t), 5.35 (2H, s), 6.79 (2H, d), 6.96 (1H, d), 7.08-7.14 (3H, m), 7.41-7.45 (1H, m), 7.93 (1H, dd)
IP		-CH ₂ -CH ₂ -O-	-I	II	Me	II	O	NH ₂	142-143	2.89 (1H, dd), 3.08 (1H, dd), 3.34 (3H, s), 3.81 (1H, dd), 3.95 (2H, t), 4.18 (2H, t), 5.32 (1H, br d), 5.37 (2H, s), 6.32 (1H, br d), 6.80 (2H, d), 6.97 (1H, dd), 7.11 (1H, dt), 7.15 (2H, d), 7.42-7.46 (1H, m), 7.95 (1H, dd)

Table 5

No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	ml. p. (°C)	NMR (CDC l ₃ , δ)
IQ		-CH ₂ -CH ₂ -O-	4	H	H	H	O	NH ₂	156-157	1.02 (3H, t), 2.70 (1H, dd), 2.84 (1H, dd), 3.22-3.30 (1H, m), 3.39-3.47 (1H, m), 3.72 (1H, d), 4.26 (2H, t), 4.37 (2H, t), 6.81-6.85 (2H, m), 7.04-7.11 (4H, m), 7.55 (1H, ddd), 7.69 (1H, dd), 7.83 (1H, ddd), 8.17 (1H, dd), 8.38 (1H, s) (DMSO-d ₆)
IR		-CH ₂ -CH ₂ -O-	4	H	H	H	O	NH ₂	amorphous	1.12 (3H, t), 2.84 (1H, dd), 3.06 (1H, dd), 3.36-3.44 (1H, m), 3.46-3.53 (1H, m), 3.86 (1H, dd), 3.90 (2H, t), 4.15 (2H, t), 5.18 (2H, s), 5.45 (1H, brs), 6.42 (1H, brs), 6.61-6.64 (2H, m), 6.90 (1H, dd), 7.00 (1H, ddd), 7.09-7.11 (2H, m), 7.14-7.18 (3H, m), 7.29 (1H, ddd), 7.32 (2H, ddd), 8.02 (1H, dd)
IS		-CH ₂ -CH ₂ -	4	H	H	H	O	NH ₂	144-145	1.01 (3H, t), 2.74 (1H, dd), 2.91 (1H, dd), 2.99 (2H, t), 3.21-3.29 (1H, m), 3.40-3.47 (1H, m), 3.77 (1H, dd), 4.20 (2H, t), 7.07-7.16 (6H, m), 7.54 (1H, ddd), 7.63 (1H, dd), 7.81 (1H, ddd), 8.13 (1H, s), 8.18 (1H, dd) (DMSO-d ₆)
IT		-CH ₂ -CH ₂ -O-	4	H	H	H	O	NH ₂	134-135	1.03 (3H, t), 2.71 (1H, dd), 2.85 (1H, dd), 3.21-3.31 (1H, m), 3.41-3.48 (1H, m), 3.53 (3H, s), 3.74 (1H, dd), 4.16 (2H, t), 4.33 (2H, t), 6.81-6.85 (2H, m), 7.05-7.11 (4H, m), 7.31 (1H, dd), 7.78 (1H, ddd), 8.07 (1H, dd) (DMSO-d ₆)

Table 6

No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDC l ₃ , δ)
IU			4	H	Et	H	O	NH ₂	183-184	1.03 (3H, t), 2.71 (1H, dd), 2.85 (1H, dd), 3.22-3.32 (1H, m), 3.41-3.48 (1H, m), 3.55 (3H, s), 3.74 (1H, dd), 3.83 (3H, s), 3.95 (3H, s), 4.15 (2H, t), 4.31 (2H, t), 6.82-6.85 (2H, m), 6.89 (1H, s), 7.05-7.11 (4H, m), 7.44 (1H, s) (DMSO-d ₆)
IV		-ClCH ₂ -ClCH ₂ -	4	H	Et	H	O	NH ₂	187-188	1.03 (3H, t), 2.76 (1H, dd), 2.83-2.87 (2H, m), 2.91 (1H, dd), 3.23-3.31 (1H, m), 3.41-3.49 (1H, m), 3.53 (3H, s), 3.78 (1H, dd), 4.12-4.16 (2H, m), 7.08-7.19 (6H, m), 7.45 (1H, dd), 7.77 (1H, ddd), 8.05 (1H, dd) (DMSO-d ₆)
IW			4	H	Et	H	O	NH ₂	112-113	1.03 (3H, t), 1.90 (2H, quin), 2.61 (2H, t), 2.73 (1H, dd), 2.87 (1H, dd), 3.25-3.50 (5H, m), 3.77 (1H, dd), 3.99 (2H, t), 7.06-7.14 (6H, m), 7.29 (1H, ddd), 7.42 (1H, dd), 7.76 (1H, dd), 8.04 (1H, dd) (DMSO-d ₆)

Table 7

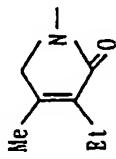
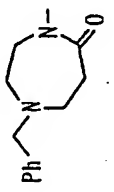
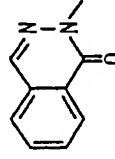
Na	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDC l ₃ , δ)
IX		-CH ₂ -CH ₂ -O-	4	H	Et	H	O	Nil ₂	131-132	1. 06 (3H, l), 1. 14 (3H, l), 1. 97 (3H, s), 2. 27 (2H, q), 2. 84-2. 90 (1H, m), 3. 05-3. 09 (1H, m), 3. 39-3. 55 (2H, m), 3. 81 (2H, l), 3. 91 (1H, dd), 3. 94 (2H, s), 4. 10 (2H, l), 5. 52 (1H, br), 6. 45 (1H, br), 6. 81 (2H, d), 7. 16 (2H, d)
IY		CH ₂ -CH ₂ -O-	4	H	Et	H	O	Nil ₂	oil	1. 14 (3H, l), 2. 58-2. 69 (6H, m), 2. 85 (1H, dd), 3. 10 (1H, dd), 3. 43-3. 61 (6H, m), 3. 75 (2H, l), 3. 90 (1H, dd), 4. 08 (2H, l), 5. 45 (1H, br), 6. 45 (1H, br), 6. 78 (2H, d), 7. 17 (2H, d), 7. 26-7. 34 (5H, m)
IZ		-CH ₂ -CH ₂ -O-	4	H	Et	H	O	Nil ₂	103-104	1. 10 (3H, l), 2. 75 (3H, d), 2. 81 (1H, dd), 3. 06 (1H, dd), 3. 33-3. 48 (2H, m), 4. 12 (1H, dd), 4. 40 (2H, l), 4. 64 (2H, l), 6. 44 (1H, m), 6. 83 (2H, d), 7. 08 (2H, d), 7. 69-7. 84 (3H, m), 8. 18 (1H, s), 8. 43-8. 45 (1H, m)

Table 8

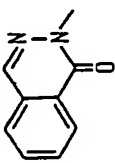
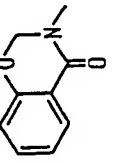
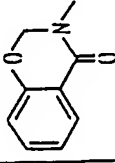
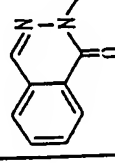

No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDCl ₃ , δ)
I AA		-CH ₂ -CH ₂ -O-	4	II	Bt	II	0	NHII	145-148	1.09(3H, l), 2.83(1H, dd), 3.07(1H, dd), 3.34-3.49(2H, m), 4.00(1H, dd), 4.40(2H, l), 4.63(2H, l), 6.83(2H, d), 7.08(2H, d), 7.69-7.84(4H, m), 8.19(1H, s), 8.42-8.44(1H, m), 8.85(1H, s)
I AB		-CH ₂ -CH ₂ -O-	4	II	Bt	3-OMe	0	NH ₂	160-161	1.13(3H, l), 2.84(1H, dd), 3.07(1H, dd), 3.39-3.53(2H, m), 3.80(3H, s), 3.87(1H, dd), 3.97(2H, l), 4.20(2H, l), 5.43(2H, s), 5.51(1H, br s), 6.45(1H, br s), 6.74-6.80(3H, m), 6.97(1H, dd), 7.10(1H, dt), 7.41-7.46(1H, m), 7.95(1H, dd)
I AC		-CH ₂ -CH ₂ -O-	4	II	Bt	3-OMe	0	OH	82-83 (Na salt)	0.98(3H, l), 2.60(1H, dd), 2.84(1H, dd), 3.09-3.18(1H, m), 3.52-3.61(1H, m), 3.70(3H, s), 3.84(2H, l), 4.08(2H, l), 5.42(2H, s), 6.69(1H, dd), 6.82-6.86(2H, m), 7.05(1H, d), 7.13-7.16(1H, m), 7.52(1H, dt), 7.81(1H, dd), (Na salt DMSO-d ₆)
I AD		-CH ₂ -CH ₂ -O-	4	II	Bt	II	0		oil	1.17(3H, l), 1.66-1.76(4H, m), 2.94-2.99(3H, m), 3.31-3.54(5H, m), 4.11(1H, l), 4.39(2H, l), 4.64(2H, l), 6.83(2H, d), 7.12(2H, d), 7.69-7.84(3H, m), 8.18(1H, s), 8.43-8.45(1H, m)

Table 9

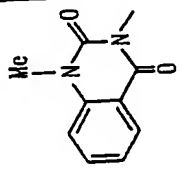
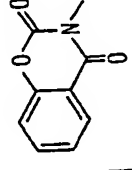
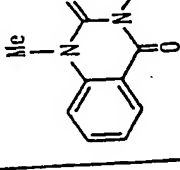
No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C.)	NMR (CDCl ₃ , δ)
1AE		-CH ₂ -CH ₂ -O-	4	II	Et	II	O	OH	89-90	1.16(3H, l), 2.91(1H, dd), 3.05(1H, dd), 3.38-3.46(1H, m), 3.55-3.63(4H, m), 4.02(1H, dd), 4.25(2H, l), 4.53(2H, l), 7.10-7.14(2H, m), 7.20-7.29(2H, m), 7.69(1H, ddd), 8.24(1H, dd)
1AP		-CH ₂ -CH ₂ -O-	4	II	Et	II	O	NH ₂	172-173	1.03(3H, l), 2.72(1H, dd), 2.86(1H, dd), 3.24-3.31(1H, m), 3.41-3.49(1H, m), 3.74(1H, dd), 4.20(2H, l), 4.26(2H, l), 6.82(2H, d), 7.06(1H, br s), 7.10-7.12(3H, m), 7.41-7.46(2H, m), 7.80-7.84(1H, m), 8.00(1H, dd) (DMSO-d ₆)
1AG		-CH ₂ -CH ₂ -O-	4	II	Et	II	O	NHCH ₃	146-148	1.09(3H, l), 2.82(1H, dd), 3.07(1H, dd), 3.34-3.38(1H, m), 3.43-3.49(1H, m), 3.61(3H, s), 3.98(1H, dd), 4.25(2H, l), 4.53(2H, l), 6.82-6.85(2H, m), 7.08-7.10(2H, m), 7.18-7.29(2H, m), 7.69(1H, ddd), 8.23(1H, dd), 8.34(1H, br), 8.90(1H, br s)

Table 10

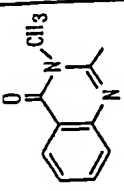
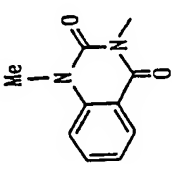
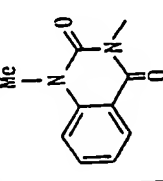
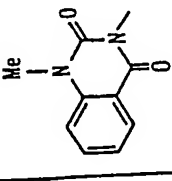
No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m.p. (°C)	NMR(CDC l ₃ , δ)
IAII		-CH ₂ -CH ₂ -O-	4	II	CH ₂ CH ₃	II	O	NH ₂	155-156.5	1.05(3H, t), 2.74(1H, dd), 2.88(1H, dd), 3.21-3.37(3H, m), 3.42-3.50(1H, m), 3.59(3H, s), 3.76(1H, dd), 4.47(2H, t), 6.87-6.91(2H, m), 7.06(1H, brs), 7.13-7.15(3H, m), 7.48(1H, ddd), 7.59(1H, dd), 7.78(1H, ddd), 8.12(1H, dd) (DMSO-d ₆)
IAI		-CH ₂ -CH ₂ -O-	4	II	CONH ₂	II	CH ₂	OH	165-168	1.07(3H, t), 2.16(1H, dd), 2.35(1H, dd), 2.65-2.76(2H, m), 2.91-2.94(1H, m), 3.53(3H, s), 3.96(2H, q), 4.16(2H, t), 4.33(2H, t), 6.69(1H, brs), 6.82-6.85(2H, m), 7.01-7.04(2H, m), 7.23(1H, brs), 7.31(1H, ddd), 7.45(1H, dd), 7.78(1H, ddd), 8.07(1H, dd) (DMSO-d ₆)
IAJ		-CH ₂ -CH ₂ -O-	4	II	CH ₂ CONH ₂	II	O	OH	142-144	1.29(3H, t), 2.89(1H, dd), 3.10(1H, dd), 3.61(3H, s), 3.79(1H, d), 4.03(1H, d), 4.20-4.29(2H, m), 4.32(2H, t), 4.52(2H, t), 5.68(1H, brs), 6.04(1H, brs), 6.87-6.90(2H, m), 7.14-7.18(2H, m), 7.22(1H, dd), 7.27(1H, ddd), 7.70(1H, ddd), 8.22(1H, dd)
IAK		-CH ₂ -CH ₂ -O-	4	II	CH ₂ CONH ₂	II	O	NH ₂	220-222	2.80(1H, dd), 2.96(1H, dd), 3.53(3H, s), 3.70-3.80(2H, m), 3.90(1H, dd), 4.16(2H, t), 4.33(2H, t), 6.82-6.86(2H, m), 6.90-7.18(5H, m), 7.31(1H, ddd), 7.46(1H, dd), 7.52(1H, brs), 7.79(1H, ddd), 8.07(1H, dd) (DMSO-d ₆)

Table 11

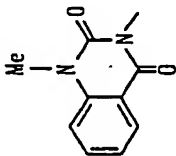
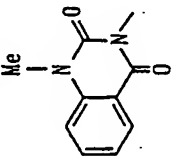
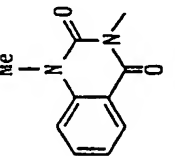
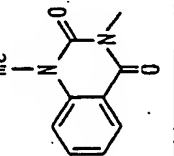
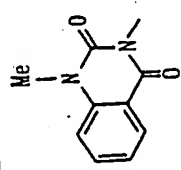
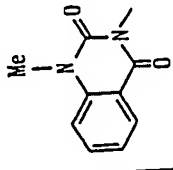
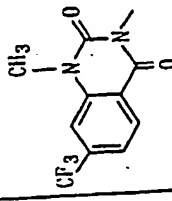
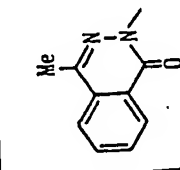
Nu	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m.p. (°C)	NMR (CDCl ₃ , δ)
I AL		-ClCH ₂ -CH ₂ -O-	4	H	CH ₂ COOMe	H	O	NH ₂	138-139.5	1.17 (3H, t), 2.81 (1H, dd), 2.93 (1H, dd), 3.53 (3H, s), 3.97 (1H, dd), 3.98 (1H, d), 4.08 (2H, q), 4.09 (1H, d), 4.16 (2H, t), 4.33 (2H, t), 6.81-6.85 (2H, m), 7.11-7.22 (4H, m), 7.31 (1H, ddd), 7.45 (1H, dd), 7.78 (1H, ddd), 8.07 (1H, dd) (DMSO-d ₆)
I AM		-ClCH ₂ -CH ₂ -O-	4	H	CH ₂ CH ₂ OH	H	O	NH ₂	144-146	2.74 (1H, dd), 2.91 (1H, dd), 3.35-3.50 (4H, m), 3.53 (3H, s), 3.81 (1H, dd), 4.16 (2H, t), 4.33 (2H, t), 4.62 (1H, t), 6.81-6.85 (2H, m), 7.10-7.13 (3H, m), 7.24 (1H, brs), 7.31 (1H, ddd), 7.45 (1H, dd), 7.78 (1H, ddd), 8.07 (1H, dd) (DMSO-d ₆)
I AN		-ClCH ₂ -CH ₂ -O-	4	H	COOMe	H	CH ₂	OMe	90-92	2.39 (1H, dd), 2.52 (1H, dd), 2.69 (1H, dd), 2.81 (1H, dd), 2.93-2.98 (1H, m), 3.53 (3H, s), 3.54 (3H, s), 3.55 (3H, s), 4.17 (2H, t), 4.33 (2H, t), 6.83-6.86 (2H, m), 7.02-7.05 (2H, m), 7.31 (1H, ddd), 7.45 (1H, dd), 7.78 (1H, ddd), 8.07 (1H, dd) (DMSO-d ₆)
I AO		-ClCH ₂ -CH ₂ -O-	4	H	CH ₂ COOMe	H	O	OMe	102-103.5	2.87-2.97 (2H, m), 3.53 (3H, s), 3.59 (3H, s), 3.61 (3H, s), 4.08 (1H, d), 4.16 (2H, t), 4.19 (1H, d), 4.26 (1H, t), 4.33 (2H, t), 6.82-6.85 (2H, m), 7.08-7.11 (2H, m), 7.31 (1H, ddd), 7.45 (1H, dd), 7.78 (1H, ddd), 8.07 (1H, dd) (DMSO-d ₆)

Table 12

No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m.p. (°C)	NMR (CDC l ₃ , δ)
IAP		-CH ₂ -CH ₂ -O-	4	H	COOH	H	CH ₂	OH	oil	1.09 (3H, t), 1.14 (3H, t), 2.37 (1H, dd), 2.49 (1H, dd), 2.69 (1H, dd), 2.80 (1H, dd), 2.91-2.95 (1H, m), 3.53 (3H, s), 2.97-4.04 (4H, m), 4.17 (2H, t), 4.33 (2H, t), 6.83-6.87 (2H, m), 7.03-7.06 (2H, m), 7.31 (1H, ddd), 7.45 (1H, dd), 7.78 (1H, ddd), 8.07 (1H, dd) (DMSO-d ₆)
IAQ		-CH ₂ -CH ₂ -O-	4	H	CH ₂ COOH	H	O	OH	oil	1.11 (3H, t), 1.17 (3H, t), 2.92 (2H, d), 3.53 (3H, s), 4.02-4.25 (9H, m), 4.33 (2H, t), 6.82-6.85 (2H, m), 7.09-7.12 (2H, m), 7.31 (1H, ddd), 7.45 (1H, dd), 7.78 (1H, ddd), 8.07 (1H, dd)
IAR		-CH ₂ -CH ₂ -O-	4	H	CH ₂ Cl ₃	H	O	OH	119-121	1.16 (3H, t), 2.92 (1H, dd), 3.06 (1H, dd), 3.40-3.48 (1H, m), 3.52-3.65 (1H, m), 3.65 (3H, s), 4.03 (1H, dd), 4.26 (2H, t), 4.54 (2H, t), 6.81-6.85 (2H, m), 7.09-7.14 (2H, m), 7.43 (1H, s), 7.51 (1H, d), 8.37 (1H, d)
IAS		-CH ₂ -CH ₂ -O-	4	H	CH ₂ COOEt	H	O	OH	110-118	1.16 (3H, t), 2.55 (3H, s), 2.80 (1H, dd), 2.93 (1H, dd), 3.97 (1H, dd), 3.98 (1H, d), 4.04 (2H, q), 4.10 (1H, d), 4.34 (2H, t), 4.36 (2H, t), 6.80-6.84 (2H, m), 7.09-7.14 (3H, m), 7.22 (1H, brs), 7.84-7.95 (3H, m), 8.30 (1H, d) (DMSO-d ₆)

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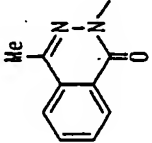
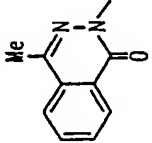
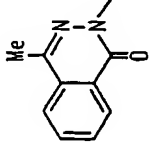
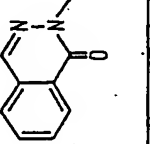

No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDC l ₃ , δ)
IAT		-Cl ₂ -Cl ₂ -O-	4	II	Cl ₂ Cl ₂ CH	II	O	NH ₂	127-128.5	2.56(3H, s), 2.73(1H, dd), 2.90(1H, dd), 3.35-3.47(4H, m), 3.80(1H, dd), 4.34(2H, t), 4.46(2H, t), 4.62(1H, t), 6.80-6.83(2H, m), 7.09-7.12(3H, m), 7.24(1H, brs), 7.85-7.95(3H, m), 8.30(1H, d) (DMSO-d ₆)
IAU		-CH ₂ -Cl ₂ -O-	4	II	CH ₂ COOMe	II	O	OMe	oil	2.55(3H, s), 2.90-2.92(2H, m), 3.58(3H, s), 3.61(3H, s), 4.08(1H, d), 4.19(1H, d), 4.25(1H, t), 4.34(2H, t), 4.46(2H, t), 6.81-6.84(2H, m), 7.07-7.10(2H, m), 7.84-7.95(3H, m), 8.28-8.31(1H, m) (DMSO-d ₆)
IAY		-Cl ₂ -Cl ₂ -O-	4	II	CH ₂ COOEt	II	O	OEt	oil	1.10(3H, t), 1.16(3H, t), 2.55(3H, t), 2.91(2H, d), 4.01-4.11(5H, m), 4.17(1H, d), 4.22(1H, t), 4.34(2H, t), 4.46(2H, t), 6.81-6.84(2H, m), 7.07-7.11(2H, m), 7.85-7.89(1H, m), 7.94-7.95(2H, m), 8.29-8.31(1H, m) (DMSO-d ₆)
IAX		-Cl ₂ -Cl ₂ -O-	4	II		II	O	OMe	104-105	3.12-3.20(2H, m), 3.69(3H, s), 4.39(2H, t), 4.63(2H, t), 4.71-4.75(1H, m), 6.79-6.96(5H, m), 7.15-7.26(4H, m), 7.67-7.83(3H, m), 8.17(1H, s), 8.42-8.45(1H, m)

Table 14

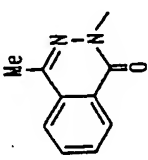

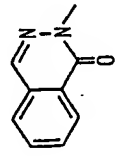

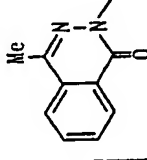

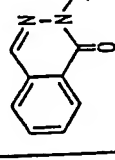

No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m.p. (°C)	NMR (CDCl ₃ , δ)
1AX		-Cl ₂ -CH ₂ -O-	4	H		H	O	OMe	138-140	2.58 (3H, s), 3.10-3.20 (2H, m), 3.69 (3H, s), 4.38 (2H, t), 4.59 (2H, t), 4.72-4.75 (1H, m), 6.79-6.96 (3H, m), 7.15-7.26 (4H, m), 7.73-7.83 (3H, m), 8.45-8.48 (1H, m)
1AY		-Cl ₂ -CH ₂ -O-	4	H		H	O	OBt	oil	1.16 (3H, t), 3.15 (2H, d), 4.11-4.71 (7H, m), 6.76-7.23 (9H, m), 7.67-7.76 (3H, m), 8.15 (1H, s), 8.30-8.50 (1H, m)
1AZ		-Cl ₂ -CH ₂ -O-	4	H		H	O	OBt	oil	1.17 (3H, t), 2.56 (3H, s), 3.15 (2H, d), 4.03-4.78 (7H, m), 6.76-7.26 (9H, m), 7.70-7.78 (3H, m), 8.40-8.50 (1H, m)
1BA		-Cl ₂ -CH ₂ -O-	4	H		H	O	OH	60-62	3.19 (2H, d), 4.37 (2H, t), 4.63 (2H, t), 4.78 (1H, t), 5.50 (1H, br), 6.82-6.97 (5H, m), 7.20-7.26 (4H, m), 7.67-7.83 (3H, m), 8.18 (1H, s), 8.42-8.44 (1H, m)

Table 15

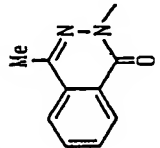

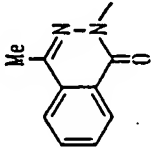
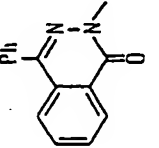
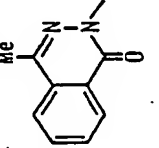

Na	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDCl ₃ , δ)
1BD		-CH ₂ -CH ₂ -O-	4	H		H	O	OH	155-159	2.57 (3H, s), 3.18 (2H, d), 4.35 (2H, t), 4.58 (2H, t), 4.76 (1H, t), 6.82-6.95 (5H, m), 7.16-7.26 (4H, m), 7.72-7.80 (3H, m), 8.44-8.46 (1H, m)
1BC		-CH ₂ -CH ₂ -O-	4	H	CH ₂ Cl ₃	H	O	OH	107-109	1.15 (3H, t), 2.59 (3H, s), 2.89-3.06 (2H, m), 3.36-3.60 (2H, m), 4.01-4.03 (1H, m), 4.38 (2H, t), 4.60 (2H, t), 6.84-6.87 (2H, m), 7.11-7.14 (2H, m), 7.74-7.84 (3H, m), 8.46-8.48 (1H, m)
1BD		-CH ₂ -CH ₂ -O-	4	H	CH ₂ Cl ₃	H	O	OH	114-118	1.14 (3H, t), 2.88-3.06 (2H, m), 3.36-3.61 (2H, m), 3.99-4.02 (1H, m), 4.44 (2H, t), 4.71 (2H, t), 6.85 (2H, d), 7.12 (2H, d), 7.52-7.59 (5H, m), 7.72-7.81 (3H, m), 8.53-8.55 (1H, m)
1BC		-CH ₂ -CH ₂ -O-	4	COOEt		H	O	OH	87-88	1.14 (3H, t), 2.61 (3H, s), 3.56 (2H, s), 4.16 (4H, q), 4.39 (2H, t), 4.61 (2H, t), 6.82-6.84 (2H, m), 6.97-7.04 (3H, m), 7.09-7.11 (2H, m), 7.24-7.29 (2H, m), 7.77-7.84 (3H, m), 8.48-8.50 (1H, m)

Table 16

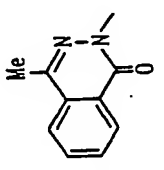

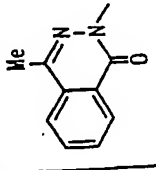
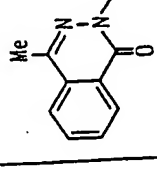
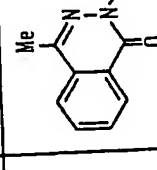
No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDC l ₃ , δ)
IBF		-Cl ₂ -Cl ₂ -O-	4	COOEt		II	O	OII	70-73	1. 04(3H, t), 2. 59(3H, s), 3. 53(2H, s), 4. 09-4. 18(2H, m), 4. 35(2H, t), 4. 57(2H, t), 6. 30(1H, br), 6. 73-7. 26(9H, m), 7. 73-7. 83(3H, m), 8. 42-8. 44(1H, m)
IBG		-CH ₂ -Cl ₂ -O-	3	II	Cl ₂ Cl ₃	II	O	OII	120-122	1. 16(3H, t), 2. 61(3H, s), 2. 95-3. 09(2H, m), 3. 41-3. 62(2H, m), 4. 06-4. 09(1H, m), 4. 41-4. 44(2H, m), 4. 57-4. 61(2H, m), 6. 80-6. 86(3H, m), 7. 15-7. 19(1H, m), 7. 76-7. 85(3H, m), 8. 46-8. 48(1H, m)
IBH		-Cl ₂ -Cl ₂ -O-	3	II	Cl ₂ Cl ₃	II	O	NII ₂	91-92	1. 11(3H, t), 2. 60(3H, s), 2. 83-2. 88(1H, m), 3. 07-3. 11(1H, m), 3. 36-3. 53(2H, m), 3. 90-3. 93(1H, m), 4. 40(2H, t), 4. 60(2H, t), 5. 46(1H, br), 6. 48(1H, br), 6. 79-6. 84(3H, m), 7. 14-7. 18(1H, m), 7. 75-7. 84(1H, m), 8. 46-8. 48(1H, m)
IBI		-Cl ₂ -Cl ₂ -O-	4	II	Cl ₂ Cl ₃	H	O	OEt	54-56	1. 15(3H, t), 1. 21(3H, t), 2. 60(3H, s), 2. 91-2. 93(2H, m), 3. 31-3. 35(1H, m), 3. 56-3. 60(1H, m), 3. 92-3. 96(1H, m), 4. 15(2H, q), 4. 39(2H, t), 4. 60(2H, t), 6. 85(2H, d), 7. 12(2H, d), 7. 75-7. 84(3H, m), 8. 46-8. 48(1H, m)

Table 17

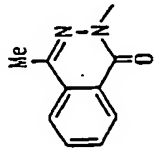
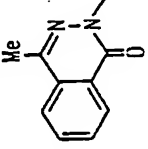
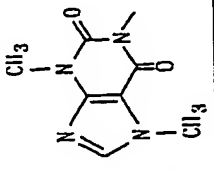
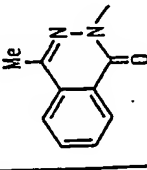
Na	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDC l ₃ , δ)
IBJ		-Cl ₂ -Cl ₂ -O-	4	II	Cl ₂ Cl ₂	II	O	OH	152-154	2.60(3H, s), 3.00-3.11(2H, m), 3.67-3.72(1H, m), 3.95-4.00(1H, m), 4.17-4.20(1H, m), 4.39(2H, t), 4.60(2H, t), 6.85(2H, d), 7.13(2H, d), 7.76-7.83(3H, m), 8.46-8.48(1H, m)
IBK		-Cl ₂ -Cl ₂ -O-	4	II	Cl ₂ Cl ₂ OCl ₃	II	O	OH	oil	2.60(3H, s), 2.84-2.90(1H, m), 3.12-3.17(1H, m), 3.39(3H, s), 3.39-3.55(4H, m), 4.02-4.05(1H, m), 4.39(2H, t), 4.60(2H, t), 6.86(2H, d), 7.14(2H, d), 7.76-7.83(3H, m), 8.46-8.48(1H, m)
IBL		-Cl ₂ -Cl ₂ -O-	4	II	Cl ₂ Cl ₂	II	O	OH	amorphous	1.16(3H, t), 2.90-3.08(2H, m), 3.41-3.47(1H, m), 3.55-3.59(1H, m), 3.57(3H, s), 3.99(3H, s), 3.99-4.04(1H, m), 4.21(2H, t), 4.45(2H, t), 6.85(2H, d), 7.13(2H, d), 7.55(1H, s)
IBM		-Cl ₂ -Cl ₂ -O-	4	II	Cl ₂ Cl ₂ OCl ₃	II	O	OMe	67-68	2.59(3H, s), 2.94-2.96(2H, m), 3.29(3H, s), 3.45-3.49(3H, m), 3.66-3.68(1H, m), 3.68(3H, s), 4.04-4.08(1H, m), 4.38(2H, t), 4.60(2H, t), 6.85(2H, d), 7.06(2H, d), 7.75-7.82(3H, m), 8.46-8.48(1H, m)

Table 18

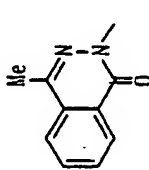
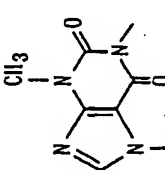
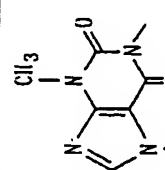
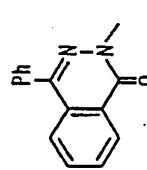
No	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDC l ₃ , δ)
1DN		-CH ₂ -CH ₂ -O-	4	H	CH ₂ CF ₃	H	O	OMe	111-112	2.59(3H, s), 2.93-3.06(2H, m), 3.62-3.72(1H, m), 3.72(3H, s), 3.93-4.03(1H, m), 4.13-4.16(1H, m), 4.39(2H, t), 4.60(2H, t), 6.85(2H, d), 7.10(2H, d), 7.74-7.83(3H, m), 8.46-8.48(1H, m)
1BO		-CH ₂ -CH ₂ -O-	4	H	CH ₂ Cl ₃	H	O	OMe	88-89	1.15(3H, t), 2.93(2H, d), 3.23-3.58(2H, m), 3.58(3H, s), 3.69(3H, s), 3.89-4.09(1H, m), 4.00(3H, s), 4.05-4.55(4H, m), 6.82(2H, d), 7.12(2H, d), 7.52(1H, s)
1BP		-CH ₂ -CH ₂ -O-	4	H	CH ₂ Cl ₃	H	O	Nil	oil	1.12(3H, t), 2.81-2.87(1H, m), 3.04-3.08(1H, m), 3.38-3.53(2H, m), 3.58(3H, s), 3.85-3.88(1H, m), 3.99(3H, s), 4.21(2H, t), 4.44(2H, t), 5.58(1H, br), 6.43(1H, br), 6.84(2H, d), 7.13(2H, d), 7.52(1H, s)
1BQ		-CH ₂ -CH ₂ -O-	4	H	CH ₂ Cl ₃	H	O	OBt	oil	1.06-1.28(6H, m), 2.92(2H, d), 3.15-3.75(2H, m), 3.86-4.26(3H, m), 4.40-4.80(4H, m), 6.79-7.17(4H, m), 7.49-7.80(8H, m), 8.45-8.60(1H, m)

Table 19

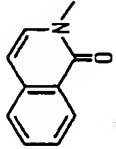
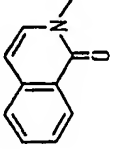
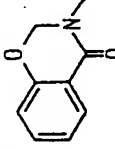
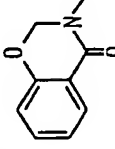
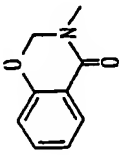
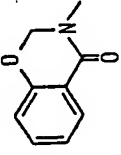
Na	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m.p. (°C)	NMR (CDCl ₃ , δ)
1BR		-CH ₂ -CH ₂ -O-	4	H	CH ₂ CH ₃	H	O	NH ₂	143-145	1.02(3H, t), 2.71(1H, dd), 2.85(1H, dd), 3.21-3.30(1H, m), 3.39-3.48(1H, m), 3.73(1H, dd), 4.25(2H, t), 4.33(2H, t), 6.62(1H, d), 6.82-6.85(2H, m), 7.03-7.11 (4H, m), 7.47-7.52(2H, m), 7.63-7.72(2H, m), 8.23(1H, d) (DMSO-d ₆)
1BS		-CH ₂ -CH ₂ -O-	4	H	CH ₂ CH ₃	H	O	OH	79-80	1.02(3H, t), 2.78(1H, dd), 2.87(1H, dd), 3.21-3.33(1H, m), 3.46-3.57(1H, m), 3.91(1H, dd), 4.25(2H, t), 4.34(2H, t), 6.62(1H, d), 6.82-6.85(2H, m), 7.09-7.13(2H, m), 7.48-7.52(2H, m), 7.63-7.72(2H, m), 8.24(1H, dd), 12.25(1H, br) (DMSO-d ₆)
1BT		-CH ₂ -CH ₂ -O-	4	H	CH ₂ CF ₃	H	O	OMe	105-106	2.99-3.04(2H, m), 3.64-3.73(4H, m), 3.94-4.02(3H, m), 4.14-4.19(3H, m), 5.36(2H, s), 6.80(2H, d), 6.97(1H, dd), 7.09-7.14(3H, m), 7.44(1H, dd), 7.95(1H, dd)
1BU		-CH ₂ -CH ₂ -O-	4	H	CH ₂ CF ₃	H	O	OH	105-107	3.01(1H, dd), 3.11(1H, dd), 3.67-3.72(1H, m), 3.93-4.00(3H, m), 4.14-4.21(3H, m), 5.36(2H, s), 6.80(2H, d), 6.97(1H, dd), 7.10(1H, dd), 7.16(2H, d), 7.44(1H, ddd), 7.94(1H, dd)

Table 20

No.	W	A	PS	R ¹	R ²	R ³	X	Y ¹	m. p. (°C)	NMR (CDCl ₃ , δ)
1DV		-ClCH ₂ -CH ₂ -O-	4	H	ClCH ₂ CH ₂ OCH ₃	H	O	OH	94-96	2.90 (III, dd), 3.16 (III, dd), 3.37-3.47 (5H, m), 3.53-3.56 (1H, m), 3.66-3.67 (1H, m), 3.95 (2H, t), 4.04 (1H, dd), 4.18 (2H, t), 5.37 (2H, s), 6.81 (2H, d), 6.97 (1H, dd), 7.10 (1H, dd), 7.17 (2H, d), 7.44 (1H, dd), 7.95 (1H, dd)
1DW		-ClCH ₂ -CH ₂ -O-	4	H	ClCH ₂ CH ₂ OCH ₃	H	O	OMe	87-88	2.95-2.98 (2H, m), 3.30 (3H, s), 3.45-3.50 (3H, m), 3.67-3.71 (4H, m), 3.95 (2H, t), 4.07 (1H, dd), 4.18 (2H, t), 5.37 (2H, s), 6.79 (2H, d), 6.97 (1H, d), 7.09-7.15 (3H, m), 7.44 (1H, dd), 7.95 (1H, dd)

[0090] The following compounds can be prepared in accordance with processes similar to the processes described in the above Preparation Examples and Examples.

- 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Methylthio-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Propylthio-3-[4-[3-(1-oxo-1,2-dihydrophthalazin-2-yl)propoxy]phenyl]propanamide;
 2-Propoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 5 2-Propoxy-3-[4-[3-(1-oxo-1,2-dihydrophthalazin-2-yl)propoxy]phenyl]propanamide;
 2-Isopropoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Isopropoxy-3-[4-[3-(1-oxo-1,2-dihydrophthalazin-2-yl)propyl]phenyl]propanamide;
 2-Phenoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Phenylthio-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 10 2-Methylamino-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Ethylamino-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Methyl-2-propoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Methyl-2-propylthio-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Methyl-2-propylamino-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 15 2-Methyl-2-isopropoxy-3-[4-[3-(1-oxo-1,2-dihydrophthalazin-2-yl)propyl]phenyl]propanamide;
 2-Ethoxy-3-[4-[2-(6-methyl-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-butoxy-3-[4-[2-(4,6-dimethyl-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[2-(6-methoxy-4-phenyl-1-oxo-1,2-dihydrophthalazin-2-yl)propoxy]phenyl]propanamide;
 2-Ethylthio-3-[4-[2-(6-methoxy-4-phenyl-1-oxo-1,2-dihydrophthalazin-2-yl)propoxy]phenyl]propanamide;
 20 2-Ethylamino-3-[4-[2-(6-methoxy-4-phenyl-1-oxo-1,2-dihydrophthalazin-2-yl)propoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[2-(6-methoxy-4-(2-pyridyl)-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Methylthio-3-[4-[2-(6-methoxy-4-(2-pyridyl)-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Methylamino-3-[4-[2-(6-methoxy-4-(2-pyridyl)-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[2-(6-methoxy-4-(4-pyridyl)-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanamide;
 25 2-Ethoxy-3-[4-[3-(4-ethyl-6-methoxy-1-oxo-1,2-dihydrophthalazin-2-yl)butoxy]phenyl]propanamide;
 N1-Ethyl-2-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)-1-methylethoxy]-3-methylbenzyl]-2-ethoxybutanamide;
 6-Chloro-2-[3-[4-(2-ethoxy-2-methyl-3-oxo-3-piperidinopropyl)phenyl]-2-methyl-3-oxopropyl]-1,2-dihydro-1-phthalazinone;
 7-Methyl-2-[3-[4-(2-ethoxy-2-methyl-3-oxo-3-pyrrolidinopropyl)phenyl]-2-hydroxypropyl]-1,2-dihydro-1-phthalazine;
 30 none;
 Ethyl 2-methylthio-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoate;
 Methyl 2-isopropoxy-3-[4-[3-(1-oxo-1,2-dihydrophthalazin-2-yl)propyl]phenyl]propanoate;
 Propyl 2-phenoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoate;
 Isopropyl 2-ethylamino-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoate;
 35 2-Isopropoxy-3-[4-[3-(1-oxo-1,2-dihydrophthalazin-2-yl)propyl]phenyl]propanoic acid;
 2-Isopropylthio-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoic acid;
 2-Isopropylamino-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[4-(1-oxo-1,2-dihydrophthalazin-2-yl)butyl]phenyl]propanoic acid;
 2-Phenoxy-3-[4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)propoxy]phenyl]propanoic acid;
 40 2-Propoxy-3-[4-[2-(5-methyl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethylthio-3-[4-[2-(5-methyl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethylamino-3-[4-[2-(5-methyl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[2-(6-acetyl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanamide;
 2-Butoxy-3-[4-[2-(6-butyryl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanamide;
 45 2-Ethylthio-3-[4-[2-(6-amino-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[2-(6-methoxy-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanamide;
 2-Ethoxy-3-[4-[3-(7-methoxy-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanamide;
 2-Ethoxy-3-[4-[3-(7-methyl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanamide;
 2-Phenoxy-3-[4-[3-(7-methyl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoate;
 50 Ethyl 2-ethoxy-3-[4-[3-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoate;
 Propyl 2-methoxy-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoate;
 Ethyl 2-phenoxy-3-[4-[3-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(7-methyl-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propoxy]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(7-chloro-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)butoxy]phenyl]propanoic acid;
 55 2-Butoxy-3-[4-[4-(7-chloro-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)butoxy]phenyl]propanoic acid;
 2-Benzoyloxy-3-[4-[3-(7-cyano-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)butoxy]phenyl]-2-ethoxy-2-methylpropanamide;
 N1-Ethyl-3-[4-[4-(7-cyano-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)butoxy]phenyl]-2-ethoxy-2-methylpropanamide;

- N1,N1-Dimethyl-3-[4-[2-(7-benzyloxy-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]-2-ethoxy-2-methylpropanamide;
- N1,N1-Diethyl-3-[4-[2-(7-benzyloxy-4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)butoxy]phenyl]-2-ethoxy-2-methylpropanamide;
- 6-Chloro-3-[3-[4-(2-ethoxy-2-methyl-3-oxo-3-piperidinopropyl)phenyl]-2-methyl-3-oxopropyl]-4-oxo-3,4-dihydro-2H-1,3-benzoxazine;
- 2-Ethoxy-3-[4-[2-(6-methyl-4-oxo-1-phenyl-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
- 2-Ethylthio-3-[4-[2-(6-methyl-4-oxo-1-phenyl-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
- 2-Methoxy-3-[4-[2-(1,6-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
- 2-Propylamino-3-[4-[3-(1,6-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanamide;
- 2-Propylthio-3-[4-[3-(1,6-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanamide;
- 2-Ethoxy-3-[4-[3-(1-ethyl-6-methoxy-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanamide;
- 2-Isopropylthio-3-[4-[2-(1-ethyl-6-methoxy-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
- N1,N1-Dimethyl-2-[4-[2-(1-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]benzyl]-2-ethoxybutanamide;
- N1,N1-Dimethyl-2-[4-[2-(1-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]benzyl]-2-ethylthiobutanamide;
- Methyl 2-ethoxy-3-[4-[2-(6-methyl-4-oxo-1-phenyl-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoate;
- Methyl 2-ethoxy-3-[4-[2-(1,6-dimethyl-4-oxo-1-phenyl-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoate;
- Isopropyl 2-ethylthio-3-[4-[2-(1-ethyl-6,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoate;
- Ethyl 2-ethylamino-3-[4-[2-(1-ethyl-6-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propoxy]phenyl]propanoate;
- 2-Ethoxy-3-[4-[3-(1-ethyl-6-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanoic acid;
- 2-Ethylthio-3-[4-[3-(1-ethyl-6-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanoic acid;
- 2-Ethylthio-3-[4-[2-(1-ethyl-6,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
- 2-Methoxy-3-[4-[2-(1-ethyl-7-methoxy-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
- 2-Propoxy-3-[4-[2-(1-ethyl-8-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
- 2-Isopropoxy-3-[4-[4-(1-ethyl-6-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)butoxy]phenyl]propanoic acid;
- 2-Ethylthio-3-[4-[2-(1-ethyl-6-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propoxy]phenyl]propanoic acid;
- 2-Ethylamino-3-[4-[2-(1-ethyl-6-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propoxy]phenyl]propanoic acid;
- 2-Ethoxy-3-[4-[4-(1,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)butanoyl]phenyl]propanoic acid;
- 2-Ethoxy-3-[4-[3-(1,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)propanoyl]phenyl]propanoic acid;
- 2-Ethylthio-3-[4-[4-(1,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)butanoyl]phenyl]propanoic acid;
- 2-Ethylamino-3-[4-[4-(1,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)butanoyl]phenyl]propanoic acid;
- 3-[4-[4-(2-Carboxy-2-ethoxybutyl)phenoxy]propyl]-7-methoxy-1-methyl-4-oxo-1,2,3,4-tetrahydro-6-quinazoline-carboxylic acid;
- 2-Isopropoxy-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
- 2-Ethylthio-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
- 2-Ethoxy-3-[4-[2-(6-methyl-4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
- N1,2-Dimethyl-2-ethoxy-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
- 2-Ethoxy-3-[4-[3-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)propyl]phenyl]propanamide;
- 2-Ethylamino-3-[4-[3-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)propyl]phenyl]propanamide;
- 2-Ethoxy-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)propyl]phenyl]propanoic acid;
- 2-Ethylthio-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanoic acid;
- 2-Ethylamino-3-[4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanoic acid;
- 2-Ethoxy-3-[4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
- 2-Propoxy-3-[4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
- 2-Ethoxy-3-[4-[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)propyl]phenyl]propanamide;
- 2-Ethylthio-3-[4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
- 2-Ethylamino-3-[4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
- N1,2-dimethyl-2-ethoxy-3-[4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
- Methyl 2-ethoxy-3-[4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl]propanoate;
- Isopropyl 2-ethoxy-3-[4-[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)propyl]phenyl]propanoate;
- 2-Ethoxy-3-[4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl]propanoic acid;
- 2-Methoxy-3-[4-[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)propyl]phenyl]propanoic acid;
- 2-Isopropoxy-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanamide;
- 2-Phenoxy-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanamide;
- 2-Propoxy-3-[4-[3-(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl]phenyl]propanamide;
- 2-Isopropylthio-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanamide;
- 2-Ethylamino-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanamide;

- N1,2-Dimethyl-2-ethoxy-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanamide;
 Ethyl 2-isopropylthio-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanoate;
 Isopropyl 2-ethylamino-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanoate;
 2-Ethoxy-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)propoxy]phenyl]propanoic acid;
 2-Isopropylthio-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanoic acid;
 2-Ethylamino-3-[4-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethoxy]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[2-(1-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 2-Methoxy-3-[4-[3-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanamide;
 2-Isopropoxy-3-[4-[2-(6,7-dimethoxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 2-Isopropylthio-3-[4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 2-Isopropylamino-3-[4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 N1,2-Dimethyl-2-ethoxy-3-[4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 2-Isopropoxy-2-methyl-3-[4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 Ethyl 2-isopropoxy-3-[4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoate;
 Propyl 2-methoxy-3-[4-[3-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanoate;
 2-Isopropoxy-3-[4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Methoxy-3-[4-[3-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)propyl]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[2-(6,7-dimethoxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Isopropoxy-2-methyl-3-[4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanamide;
 2-Propoxy-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanamide;
 2-Ethoxy-2-methyl-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanamide;
 2-Ethylthio-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanamide;
 2-Ethylamino-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanamide;
 Methyl 2-isopropoxy-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanoate;
 Ethyl 2-ethoxy-2-methyl-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoate;
 2-Isopropoxy-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Propoxy-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoic acid;
 2-Ethoxy-2-methyl-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoic acid;
 2-Ethylthio-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoic acid;
 2-Ethylamino-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)propyl]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)propyl]phenyl]propanamide;
 2-Ethylthio-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethylamino-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
 N1,2-Dimethyl-2-ethoxy-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanamide;
 Methyl 2-ethoxy-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanoate;
 Propyl 2-ethylthio-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanoate;
 2-Ethoxy-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)propyl]phenyl]propanoic acid;
 2-Ethylthio-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Ethylamino-3-[4-[2-(2,4-dioxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 2-Phenoxy-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 2-Methyl-2-propoxy-3-[4-[3-(4-oxo-3,4-dihydroquinazolin-3-yl)propyl]phenyl]propanamide;
 2-Isopropylthio-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethylamino-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanamide;
 N1,2-Dimethyl-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]-2-ethoxypropanamide;
 Methyl 2-ethoxy-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanoate;
 Ethyl 2-isopropylthio-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanoate;
 Ethyl 2-ethylamino-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanoate;
 2-Ethoxy-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(4-oxo-3,4-dihydroquinazolin-3-yl)propyl]phenyl]propanoic acid;

- 2-Isopropylthio-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Ethylamino-3-[4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Methyl-2-propoxy-3-[4-[3-(4-oxo-3,4-dihydroquinazolin-3-yl)propyl]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
 2-Phenoxy-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
 2-Methyl-2-propoxy-3-[4-[3-(1-oxo-1,2-dihydroisoquinolin-2-yl)propyl]phenyl]propanamide;
 2-Isopropylthio-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
 2-Ethylamino-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanamide;
 N1,2-Dimethyl-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]-2-ethoxypropanamide;
 Methyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanoate;
 Ethyl 2-isopropylthio-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanoate;
 2-Ethoxy-3-[4-[3-(1-oxo-1,2-dihydroisoquinolin-2-yl)propyl]phenyl]propanoic acid;
 2-Isopropylthio-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanoic acid;
 2-Ethylamino-3-[4-[2-(1-oxo-1,2-dihydroisoquinolin-2-yl)ethoxy]phenyl]propanoic acid;
 2-Methyl-2-propoxy-3-[4-[3-(1-oxo-1,2-dihydroisoquinolin-2-yl)propyl]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[3-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)propyl]phenyl]propanamide;
 2-Isopropoxy-3-[4-[3-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)propyl]phenyl]propanamide;
 2-Ethylthio-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethylamino-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanamide;
 2-Ethoxy-2-methyl-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanamide;
 N1,2-Dimethyl-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]-2-ethoxypropanamide;
 Methyl 2-ethoxy-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanoate;
 Ethyl 2-ethylthio-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanoate;
 Ethyl 2-ethoxy-2-methyl-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanoate;
 2-Ethoxy-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)propyl]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[3-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)propyl]phenyl]propanoic acid;
 2-Ethylthio-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Ethylamino-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Ethoxy-2-methyl-3-[4-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethoxy]phenyl]propanoic acid;
 2-Methoxy-3-[4-[2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)ethoxy]phenyl]propanamide;
 2-Isopropoxy-3-[4-[2-(3,4-dimethyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)ethoxy]phenyl]propanamide;
 2-Isopropoxy-3-[4-[3-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)propyl]phenyl]propanamide;
 2-Isopropylthio-3-[4-[3-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)propyl]phenyl]propanamide;
 2-Isopropylamino-3-[4-[2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)ethoxy]phenyl]propanamide;
 Ethyl 2-methoxy-3-[4-[2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)ethoxy]phenyl]propanoate;
 Methyl 2-isopropylthio-3-[4-[3-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)propyl]phenyl]propanoate;
 2-Methoxy-3-[4-[2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)ethoxy]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[2-(3,4-dimethyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)ethoxy]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[3-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)propyl]phenyl]propanoic acid;
 2-Isopropylthio-3-[4-[3-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)propyl]phenyl]propanoic acid;
 2-Isopropylamino-3-[4-[2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-1-pyrrolyl)ethoxy]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]propanamide;
 2-Ethoxy-3-[4-[3-(4-methyl-7-oxo-1,4-diazepan-1-yl)propyl]phenyl]propanamide;
 2-Isopropoxy-3-[4-[3-(4-ethyl-7-oxo-1,4-diazepan-1-yl)propyl]phenyl]propanamide;
 2-Ethylthio-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]propanamide;
 2-Ethylamino-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]propanamide;
 N1,2-Dimethyl-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]-2-ethoxypropanamide;
 2-Ethoxy-3-[4-[2-(7-oxo-4-phenyl-1,4-diazepan-1-yl)ethoxy]phenyl]propanamide;
 Ethyl 2-ethoxy-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]propanoate;
 Methyl 2-ethylthio-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]propanoate;
 2-Ethoxy-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(4-methyl-7-oxo-1,4-diazepan-1-yl)propyl]phenyl]propanoic acid;
 2-Ethoxy-3-[4-[3-(4-benzyl-7-oxo-1,4-diazepan-1-yl)propyl]phenyl]propanoic acid;
 2-Isopropoxy-3-[4-[3-(4-ethyl-7-oxo-1,4-diazepan-1-yl)propyl]phenyl]propanoic acid;
 2-Ethylthio-3-[4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl]propanoic acid;

2-Ethylamino-3-{4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl}propanoic acid;
 2-Ethoxy-2-methyl-3-{4-[2-(4-methyl-7-oxo-1,4-diazepan-1-yl)ethoxy]phenyl}propanoic acid;
 2-Ethoxy-3-{4-[2-(7-oxo-4-phenyl-1,4-diazepan-1-yl)ethoxy]phenyl}propanoic acid;
 2-Isopropylthio-3-{4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl}propanohydroxamic acid;
 5 2-Ethylamino-3-{4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl}propanohydroxamic acid;
 2-Propoxy-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propanohydroxamic acid;
 2-Propylthio-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propanohydroxamic acid;
 2-Ethoxy-3-{4-[2-(4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl}propanohydroxamic acid;
 2-Propoxy-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzthiazin-3-yl)ethoxy]phenyl}propanohydroxamic acid;
 10 2-Ethoxy-3-{4-[2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]phenyl}propanohydroxamic acid;
 2-Isopropoxy-3-{4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl}propanohydroxamic acid;
 2-Ethoxycarbonyl-2-methoxy-3-{4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl}propanamide;
 N-Methyl-2-ethoxy-2-ethoxycarbonyl-3-{4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenyl}propanamide;
 2-Propoxy-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]benzyl}malonamide;
 15 Dimethyl 2-methoxy-3-{4-[2-(1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]benzyl}malonate;
 Diethyl 2-propylthio-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]benzyl}malonate;
 Diethyl 2-ethoxy-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]benzyl}malonate;
 2-Ethoxycarbonyl-2-methoxy-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propanamide;
 N-Methyl-2-ethoxy-2-ethoxycarbonyl-3-{4-[2-(4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl)ethoxy]phenyl}propana-
 20 mide;
 2-Ethoxycarbonyl-2-isopropoxy-3-{4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl}propanamide;
 Diethyl 2-ethoxy-3-{4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]benzyl}malonate;
 2-Ethoxycarbonyl-2-methoxy-3-{4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl}propanamide;
 2-Ethoxy-3-{4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]benzyl}malonamide;
 25 N-Methyl-2-ethoxy-2-ethoxycarbonyl-3-{4-[2-(4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl}propanamide;
 2-Ethoxycarbonyl-2-isopropoxy-3-{4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phenyl}pro-
 panamide;
 Diethyl 2-ethoxy-3-{4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]benzyl}malonate;
 2-Ethoxy-3-{4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]benzyl}malonamide; and
 30 N-Methyl-2-ethoxy-2-ethoxycarbonyl-3-{4-[2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)ethoxy]phe-
 nyl}propanamide.

Test Example 1:

35 Antidiabetic effect on diabetic model mice:

[0091] The α -substituted phenylpropionic acid derivatives (1) according to the present invention were used to conduct a test for evaluating their activities against model mice suffering from non-insulin dependent diabetes mellitus (NIDDM). Incidentally, pioglitazone was used as a comparative compound.

40

(Testing method)

[0092] db/db Mice (Crea Co.; preliminarily rearing male mice aged 7 to 9 weeks for a week and using 4 or 5 mice having a blood glucose level of at least 300 mg/dl as a group) were used as subject animals. A predetermined amount of each of the compounds according to the present invention or the comparative compound was orally administered to the mice for 4 days once a day with the compound suspended in a 0.5% aqueous solution of sodium carboxymethyl cellulose. At 18 to 24 hours after the final administration, blood was collected from each of the subject animals to determine its blood glucose level (found value) by means of a simplified blood glucose meter, Mediace (manufactured by Terumo Corporation). On the other hand, the blood glucose level of a group of mice (control group) to which only a 0.5% aqueous solution of sodium carboxymethyl cellulose had been administered was also determined (control value).

50 [0093] On the basis of the thus-determined blood glucose level as to each of the compounds according to the present invention and the comparative compound, percent reduction of blood glucose was calculated out in accordance with the following equation. The results are shown in the following Table 21.

55

$$\text{Percent reduction (\%)} = \frac{[(\text{Control value} - \text{Found value})/(\text{Control value})] \times 100}{}$$

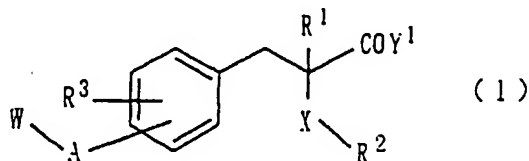
Table 21

Compound	Dose (mg/kg/day)	Percent reduction (%)	Compound	Dose (mg/kg/day)	Percent reduction (%)
1A	50	73	1W	50	50
1B	20	43	1X	50	60
1J	20	73	1AA	20	48
1K	50	69	1AR	20	38
1N	50	72	1BC	10	50
1O	50	42	1BI	20	52
1P	50	66	1BS	20	60
1Q	50	49	Pioglitazone	20	26
1T	50	53	Pioglitazone	50	44

[0094] As apparent from the results shown in the table, the compounds according to the present invention have an excellent antidiabetic effect.

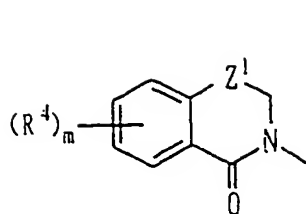
Claims

1. An α -substituted phenylpropionic acid derivative represented by the following general formula (1):

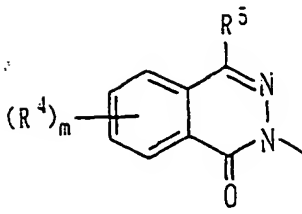


wherein W is a monocyclic or bicyclic lactam ring which may be substituted, A is an alkylene, alkyleneoxy or alkylencarbonyl group which may be substituted by at least one hydroxy group, X is O, S, NH or CH₂, Y¹ is an amino, hydroxyamino, hydroxyalkylamino, monoalkylamino, dialkylamino, cyclic amino, hydroxy or lower alkoxy group, R¹ is a hydrogen atom, lower alkyl group, hydroxyalkyl group, alkoxyalkyl group, halogenoalkyl group or COY² (in which Y² is an amino, hydroxyamino, hydroxyalkylamino, monoalkylamino, dialkylamino, cyclic amino, hydroxy or lower alkoxy group), R² is a lower alkyl, hydroxyalkyl, alkoxyalkyl or halogenoalkyl group, COY² (in which Y² has the same meaning as defined above), or a phenyl, pyridyl or aralkyl group which may be substituted, and R³ is a hydrogen or halogen atom, or an alkyl, alkoxy, halogenoalkyl, amino, hydroxy or acyl group, or a salt thereof.

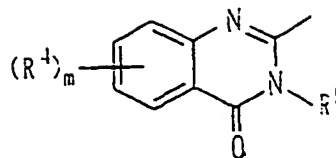
2. The α -substituted phenylpropionic acid derivative or the salt thereof according to Claim 1, wherein W in the general formula (1) is selected from among groups represented by the following (W-1) to (W-9):



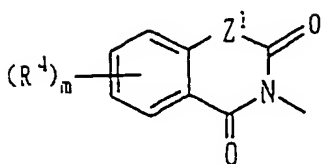
(W-1)



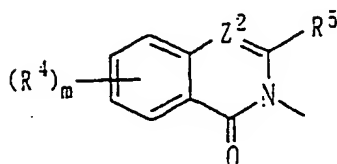
(W-2)



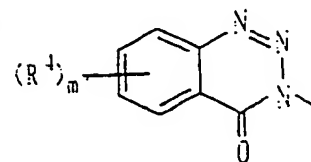
(W-3)



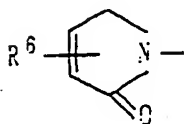
(W-4)



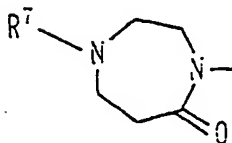
(W-5)



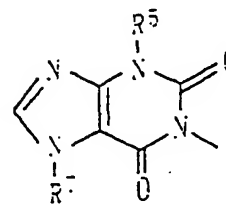
(W-6)



(W-7)



(W-8)



(W-9)

wherein R^4 is a hydrogen or halogen atom, an alkyl, alkoxy, halogenoalkyl, amino, hydroxy, cyano, carbamoyl, acyl, nitro, carboxy or sulfonamide group, or a phenyl or benzyloxy which may be substituted, R^5 is a hydrogen atom, an alkyl group, or an aryl, aralkyl or pyridyl group which may be substituted, R^6 is a hydrogen atom or a lower alkyl group, R^7 is a lower alkyl, phenyl or aralkyl group, Z^1 is O, S, CH_2 or NR^5 (in which R^5 has the same meaning as defined above), Z^2 is N or CH, and m is an integer of 1 to 4.

3. A medicine comprising the α -substituted phenylpropionic acid derivative or the salt thereof according to Claim 1 or 2 as an active ingredient.
4. The medicine according to Claim 3, which is an antidiabetic.
5. The medicine according to Claim 3, which is an agent for lowering lipid.
6. A medicinal composition comprising the α -substituted phenylpropionic acid derivative or the salt thereof according to Claim 1 or 2 and a pharmaceutically acceptable carrier.
7. Use of the α -substituted phenylpropionic acid derivative or the salt thereof according to Claim 1 or 2 for a medicine.



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EUROPEAN SEARCH REPORT

Application Number
EP 98 11 7153

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	EP 0 779 279 A (BAYER) 18 June 1997 * the whole document *	1-7	C07D237/32 C07D239/88 C07D265/22
A	WO 97 31907 A (GLAXO) 4 September 1997 * page 125; claims; example 124 *	1-7	C07D401/04 C07D239/96 C07D243/08
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D,A	CHEMICAL ABSTRACTS, vol. 126, no. 9, 3 March 1997 Columbus, Ohio, US; abstract no. 117964d, page 589; XP002032261 * abstract * & JP 08 325264 A (SUMITOMO)	1-7	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C07D A61K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 18 December 1998	Examiner Francois, J
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date O : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/42, 31/44, 31/00	A1	(11) International Publication Number: WO 97/25042 (43) International Publication Date: 17 July 1997 (17.07.97)
(21) International Application Number: PCT/EP97/00058 (22) International Filing Date: 7 January 1997 (07.01.97) (30) Priority Data: 9600464.3 9 January 1996 (09.01.96) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): SMITH, Stephen, Alistair [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF AN ANTAGONIST OF PPAR-ALPHA AND PPAR-GAMMA FOR THE TREATMENT OF SYNDROM X (57) Abstract A method for the treatment and/or prophylaxis of Syndrome X in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically effective amount of an agonist of PPAR α and PPAR γ , or a pharmaceutically acceptable derivative thereof, to a human or non-human mammal in need of such treatment, and certain compound for use in such method.		

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USE OF AN ANTAGONIST OF PPAR-ALPHA AND PPAR-GAMMA FOR THE TREATMENT OF SYNDROM X

This invention relates to a novel method of treatment, in particular for the treatment of Syndrome X and certain compounds used in said method.

5 It is known that the γ -isoform of peroxisome proliferator-activated receptor (herein after PPAR γ) is member of a nuclear receptor superfamily that includes receptors for the steroid, thyroid and retinoid hormones(Evans, Science 240, 889-895, (1988)). It is also known from Chawla *et al* that PPAR γ is expressed early during the differentiation of adipocytes (Endocrinology 135,798-10 800, 1994).

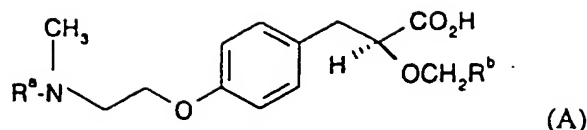
Spiegelman *et al* state in Cell (Vol 83, 803-812, 1995) that signals which modulate PPAR γ activity may serve a primary role in regulating energy homeostasis. They conclude (ibid, 810) that 'screening for potent PPAR γ agonists and antagonists represents a logical and potentially rapid approach towards the development of novel therapeutic agents for NIDDM and obesity respectively.' 15

It is known that the α -isoform of peroxisome proliferator-activated receptor (herein after PPAR α) acts to stimulate peroxisomal proliferation in the rodent liver which leads to enhanced fatty oxidation by this organ (Keller and Wahli: Trends Endocrin Metab 1993;4:291-296). Hypolipidaemic agents have the ability to stimulate PPAR alpha and the ensuing stimulation of peroxisomal proliferation and consequent fatty acid oxidation can account for the reduction in plasma fatty acids (Macdonald and Lane : Current Biology Vol5 pp618-621 20 (1995)).

Syndrome X is the syndrome characterised by an initial insulin resistant state, generating hyperinsulinaemia, dyslipidaemia and impaired glucose tolerance, which can progress to non-insulin dependent diabetes mellitus (Type II diabetes), characterised by hyperglycaemia and which then further progresses to diabetic complications. 25

We now consider that inclusion of PPAR α effects in a PPAR γ antihyperglycaemic agent will result in a reagent with enhanced therapeutic potential in the syndrome X aetiology due to an enhanced hypolipidaemic effect. 30

International Patent Application number PCT/EP 95/03038 discloses certain compounds of formula (A):



or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein R^a represents 2-benzoxazolyl or 2-pyridyl and R^b represents CH_2OCH_3 or CF_3 .

The compounds of formula (A) are stated to be of potential use in the treatment and/or prophylaxis of hyperglycaemia, especially in Type II diabetes, hyperlipidaemia, hypertension, cardiovascular disease, especially atherosclerosis and of renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease and for the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

It has now been discovered that the compounds of formula (A) exhibit agonist activity at both $\text{PPAR}\alpha$ and $\text{PPAR}\gamma$ and that as well as being particularly effective for the treatment and/or prophylaxis of hyperglycaemia they are also now considered to be most effective for the treatment and/or prophylaxis of pre-diabetic insulin resistance syndrome and the resulting complications thereof: They are therefore considered to be useful for the treatment and/or prophylaxis of insulin resistance, diabetes, dyslipidaemia, atherosclerosis, hypertension, cardiovascular disease and obesity.

Accordingly, in a first aspect the invention provides a method for the treatment and/or prophylaxis of Syndrome X in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically effective amount of an agonist of $\text{PPAR}\alpha$ and $\text{PPAR}\gamma$, or a pharmaceutically acceptable derivative thereof, to a human or non-human mammal in need of such treatment.

Thus, one aspect of the invention is the treatment of Syndrome X.

A further aspect of the invention is the prophylaxis of Syndrome X.

In particular, there is provided a method for the treatment and/or prophylaxis of hyperglycaemia.

In particular there is provided a method for the treatment of pre-diabetic insulin resistance syndrome and the resulting complications thereof.

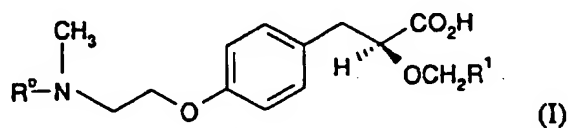
Pre-diabetic insulin resistance syndrome includes hyperinsulinaemia and impaired glucose tolerance.

In a further aspect, there is provided a method for the treatment and/or prophylaxis of Syndrome X, including hyperglycaemia and/or pre-diabetic insulin resistance syndrome and the resulting complications thereof, in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically effective amount of an agonist of PPAR α and PPAR γ , or a pharmaceutically acceptable derivative thereof, to a human or non-human mammal in need thereof; providing the method does not include the administration of:

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid; or
(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid, for the treatment and/or prophylaxis of:
hyperglycaemia, especially in Type II diabetes, hyperlipidaemia, hypertension, cardiovascular disease, especially atherosclerosis and of renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease and for the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

It will be appreciated that in its preferred form the agonist of PPAR α and PPAR γ is a single compound (such compound being referred to herein as a 'PPAR α and γ agonist') but it is within the ambit of this invention that the agonist of PPAR α and PPAR γ is provided by a combination of a PPAR α agonist compound and a PPAR γ agonist compound.

One combined PPAR α and γ agonist is a compound of formula (I):



or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein R⁰ represents 2-benzoxazolyl or 2-pyridyl and R¹ represents CH₂OCH₃ or CF₃.

Preferably, R⁰ represents 2-benzoxazolyl.

Suitably, R¹ represents CH₂OCH₃.

Preferably, R¹ represents CF₃.

The compounds of formula (I), and the pharmaceutically acceptable salts thereof, may exist in one of several tautomeric forms, all of which are
5 encompassed by the present invention as individual tautomeric forms or as mixtures thereof.

Pharmaceutically acceptable derivatives include pharmaceutically acceptable salts and solvates.

Suitable pharmaceutically acceptable salts include salts of carboxy groups
10 and acid addition salts.

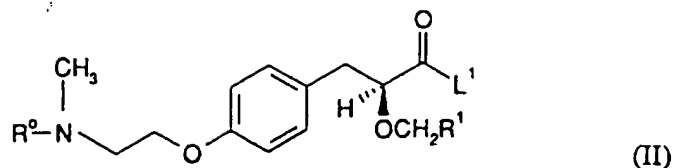
Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower
15 alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the
20 pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and, where feasible, pharmaceutically acceptable organic acid
25 addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphonate, α-keto glutarate and α-glycerophosphate.

Suitable pharmaceutically acceptable solvates include hydrates.

The pharmaceutically acceptable derivatives, such as the salts and/or solvates of the compounds of formula (I) may be prepared and isolated according to conventional procedures, for example sodium salts may be prepared by using
30 sodium methoxide in methanol.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, may be prepared by hydrolysing a compound of formula (II):



wherein R^0 and R^1 are as defined in relation to formula (I) and L^1 represents a hydrolysable group; and thereafter, if required, preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

A suitable hydrolysable group L^1 is a group of formula (a) or an epimer thereof:



A suitable hydrolysable group L^1 is an Evans chiral auxiliary, for example a group of formula (b) or an epimer thereof:

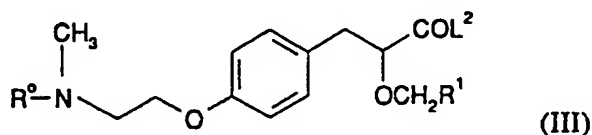


A suitable hydrolysable group L^1 is a C_{1-6} alkoxy group.

The hydrolysis of the compound of formula (II) is carried out using conditions appropriate for hydrolysing the particular group L^1 chosen, for example when L^1 is a group of formula (a) or a C_{1-6} alkoxy group, the hydrolysis is suitably carried out under acidic conditions, for example using dilute sulphuric acid, conveniently in a water/dioxan mixture, for example a 1:1 mixture, at any temperature which provides a suitable rate of formation of the required product, generally at an elevated temperature, such as in the range of from 50°C to 120°C, for example 90°C; or when L^1 is a group of formula (b) the hydrolysis is generally carried out using lithium hydroperoxide in an aqueous

solvent, such as aqueous tetrahydrofuran, at any temperature which provides a suitable rate of formation of the required product, generally at a reduced temperature, such as in the range of from -10°C to 0°C , for example 0°C . Alternatively, when L^1 is a group of formula (b) the hydrolysis may be effected under basic conditions, using for example aqueous sodium hydroxide, in an appropriate solvent such as aqueous tetrahydrofuran usually at ambient temperature.

A compound of formula (II), wherein L^1 is a moiety of the above defined formula (a) or (b), may be prepared from a compound of formula (III) :



wherein R^0 and R^1 are as defined in relation to formula (I) and L^2 represents a leaving group; (i) for compounds of formula (II) wherein L^1 is a moiety of the above defined formula (a), by reaction with (*S*)-phenylglycinol; or
 15 (ii) for compounds of formula (II) wherein L^1 is a moiety of the above defined formula (b), by reaction with (*S*)-4-benzyloxazolidin-2-one, preferably an activated form thereof; and thereafter separating the required isomer from the mixture of diastereoisomers produced.

20 A suitable leaving group L^2 is a halogen atom, for example a chlorine atom.

The reaction between the compounds of formula (III) and (*S*)-phenylglycinol may be carried out under conventional amidation conditions, for example in an inert solvent such as dichloromethane at a temperature which provides a suitable rate of formation of the required product, suitably at ambient
 25 temperature and preferably in the presence of a base such as triethylamine.

A suitable activated form of (*S*)-4-benzyloxazolidin-2-one is a salted form, for example an alkali metal salted form, preferably a lithium salt.

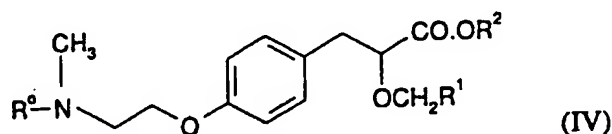
The activated form of (*S*)-4-benzyloxazolidin-2-one may be prepared by any appropriate conventional method. Thus when the activated form is a lithium
 30 salt, it may be prepared by treating (*S*)-4-benzyloxazolidin-2-one with a source of lithium ions in the presence of a base, suitably provided by *n*-butyllithium, in an

aprotic solvent such as tetrahydrofuran, usually at a low temperature, for example in the range of from -78° to 0°C .

The reaction between the compound of formula (III) and the activated form of (S)-4-benzyloxazolidin-2-one may be carried out in an aprotic solvent, such as tetrahydrofuran, at a temperature which provides a suitable rate of formation of the required product, conveniently by allowing the reaction mixture to slowly warm from -78° to 0°C .

Preferably, the activated form of (S)-4-benzyloxazolidin-2-one is prepared and then reacted *in-situ* with the compound of formula (III).

A compound of formula (III) may be prepared by hydrolysing the carboxylic ester COOR^2 of a compound of formula (IV):



wherein R^0 and R^1 are as defined in relation to formula (I) and R^2 represents an alkyl group, and thereafter converting the carboxylic acid group so formed into a moiety COL^2 .

A suitable alkyl group R^2 is a C_{1-6} alkyl group, especially a methyl group.

The hydrolysis of the carboxylic ester may be effected by use of any conventional hydrolysing agent, such as an alkaline metal hydroxide, for example sodium hydroxide.

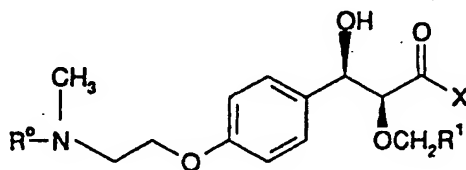
The hydrolysis of the compound of formula (IV) may be carried out in any suitable solvent such as a methanol/water mixture, conveniently a 1:1 mixture, at a temperature which provides a suitable rate of formation of the required product, suitably at an elevated temperature and conveniently at the reflux temperature of the solvent.

The conversion of the carboxylic acid group into the moiety COL^2 may be carried out using any appropriate conventional procedure, depending upon the particular nature of the group L^2 chosen, thus when L^2 is a halogen a suitable procedure involves treatment of the carboxylic acid with an oxalyl halide, for example oxalyl chloride when L^2 is chlorine.

The reaction conditions for the conversion of the carboxylic acid group into the moiety CO.L^2 will be dictated by the particular nature of L^2 and the source of L^2 chosen, for example when L^2 is halogen and the source of L^2 is oxalyl chloride then the reaction may be carried out in an inert solvent such as dichloromethane or benzene at a temperature which provides a suitable rate of formation of the required product, suitably at ambient temperature or at an elevated temperature such as the reflux temperature of the solvent.

It will be appreciated that the preparation and separation of a compound of formula (II) wherein L^1 is an epimer of the above defined moiety (a) or (b) and its subsequent hydrolysis to afford a compound of formula (I) can be achieved by employing analogous methods to those described above for the preparation, separation and hydrolysis of a compound of formula (II) wherein L^1 represents the above defined moiety (a) or (b).

A compound of formula (II) wherein L^1 is a moiety of formula (b) may also be prepared by dehydroxylation of a compound of formula (V):



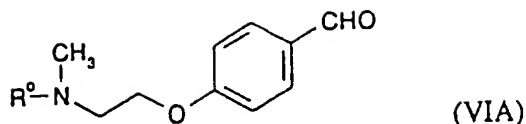
(V)

wherein R^0 and R^1 are as defined in relation to formula (I) and X is a moiety of the above defined formula (b).

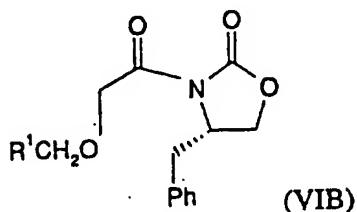
The dehydroxylation of the compound of formula (V) is conveniently carried out by treatment with a trialkylsilane, for example triethylsilane, preferably in the presence of trifluoroacetic acid and conveniently using trifluoroacetic acid as solvent, at any temperature providing a suitable rate of formulation of the product, for example at a temperature in the range from 0°C to room temperature.

It will be appreciated that a compound of formula (II) wherein L^1 is a moiety of formula (b) would also be obtained by dehydroxylation of a compound of formula (V) in which the hydroxy bearing stereocentre is epimerised.

A compound of formula (V) may be prepared by reacting a compound of formula (VIA):



- 5 wherein R^O is as defined in relation to formula (I), with a compound of formula (VIB):



- 10 wherein R^1 is as defined in relation to formula (I); and thereafter separating the required isomer from the mixture of diastereoisomers produced.

Suitably in the above mentioned reaction, the compound of formula (VIB) is in an activated form, which is preferably provided by treating the compound of formula (VIB) with an alkylboron triflate, for example dibutylboron triflate, preferably in the presence of an amine base such as triethylamine.

- 15 The activated form of the compound of formula (VIB) may be prepared by the appropriate conventional method depending upon the specific nature of the activated form chosen, for example the compound of formula (VIB) is reacted with dibutylboron triflate and triethylamine in an inert solvent such as dichloromethane at a temperature in the range of from -78° to 0°C .

The reaction between the compounds of formulae (VIA) and (VIB) may be carried out in an inert solvent such as dichloromethane, at a temperature which provides a suitable rate of formation of the required product, conveniently by allowing the reaction mixture to slowly warm from -78° to 0°C .

- 25 Preferably, the activated form of the compound of formula (VIB) is prepared and then reacted *in-situ* with the compound of formula (VIA).

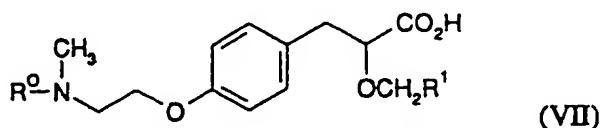
For compounds of formula (I) wherein R^O represents 2-benzoxazolyl, a suitable compound of formula (VIA) is 4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]benzaldehyde.

A suitable means for separating any required single isomer from a mixture of diastereoisomers is chromatography, such as preparative high pressure liquid chromatography or silica gel column chromatography.

One convenient method for preparing a compound of formula (II) wherein L^1 is a C_{1-6} alkoxy group is the basic alcoholysis of a compound of formula (II) wherein L^1 is a moiety of formula (b).

A suitable base is an alkali metal alkoxide, for example when L^1 is methoxy the compound of formula (II) wherein L^1 is moiety (b) is treated with sodium methoxide in methanol.

A compound of formula (I) may also be prepared by resolving a racemic compound of formula (VII):



wherein R^0 and R^1 are as defined in relation to formula (I); and thereafter, if required, preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The resolution of a compound of formula (VII) may be carried out using known resolution procedures, for example by reacting the compound of formula (VII) with a resolving agent, such as an optically active acid or base, to provide a mixture of diastereoisomeric salts which may then be separated by fractional crystallisation and thereafter the compound of formula (I) may be regenerated from the separated diastereoisomer salt by conventional means, such as hydrolysis.

It will be appreciated that the compounds of formula (VII) comprise the compounds of formula (I) admixed with other optical isomers. A compound of formula (VII) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, forms a further aspect of the present invention. The separated isomers of the compounds of formula (VII), in addition to the compounds of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, also comprise the present invention.

Suitable acids or bases for resolving the compounds of formula (VII) are as described in *Enantiomers, Racemates and Resolution*, J Jaques *et al.*, 1981,

Wiley Interscience, especially at pages 255 and 256. Suitable methods for effecting the resolution are also disclosed by Jaques *et al.*

5 The compounds of formula (IV) and (VIA), for example 4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]benzaldehyde, are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in International Patent Application, Publication Number WO94/01420.

10 The compounds of formula (VIB) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in Organic Synthesis Vol. 68, p83, 1990 Ed. J.D. White or methods analogous thereto, in combination with conventional methodology for the preparation of acid chlorides.

15 It will be appreciated that in any of the abovementioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

20 It will be appreciated that the above mentioned preparation of the compounds of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, is a stereoselective procedure and that the compound of formula (I) is a single stereoisomer. Favourably a compound of formula (I) is present in admixture with less than 50% w/w of its racemic isomer, that is when it is greater than 50% optically pure, suitably 80-
25 100% and preferably 90-100% pure, such as 90-95%, most preferably 95-100%, for example 95%, 96%, 97%, 98%, 99% or 99.9% optically pure.

Preferably the compound of formula (I) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, is in optically pure form.

30 The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

When the agonist of PPAR α and PPAR γ is provided by the combination of a PPAR α agonist compound and a PPAR γ agonist compound, a suitable PPAR γ agonist compound is selected from EP 0306228 and WO94/05659, the contents
35 of which are incorporated herein by reference.

Suitable, favoured and preferred PPAR γ agonists are those suitable, favoured and preferred compounds disclosed in EP 0306228 and WO94/05659.

A most preferred PPAR γ agonist from EP 0306228 and WO94/05659 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, especially a maleic acid salt thereof, and/or a pharmaceutically acceptable solvate thereof.

Additional PPAR γ agonists include the thiazolidinediones disclosed in European Patent Applications, Publication Numbers:0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734 and 0508740; and from International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and from United States Patent Number 5104888; the contents of these publications are also included herein by reference.

When the agonist of PPAR α and PPAR γ is provided by the combination of a PPAR α agonist compound and a PPAR γ agonist compound, suitable PPAR α agonist are the fibrates such as clofibrate, ciprofibrate, Wy 14643 and BR-931 (Lalwani *et al*, Biochemical and Biophysical Research commun., Vol. 116, 388-393, 1983); the contents of these publications are included herein by reference. The said fibrates are known compounds prepared using known methodology or analogous methodology to that use to prepare known, analogous compounds, for example the method of d'Atri *et al* J. Med. Chem., Vol 27, 1621-1629, 1984 is generally applicable to each of the mentioned fibrates.

Also specifically included in the method of the invention are the specific examples disclosed in the above mentioned publications including the patent applications.

The active compounds disclosed in the above mentioned published patent publications, including the specific examples disclosed therein, are conveniently prepared according to the methods disclosed in the said patent publications: For example a PPAR γ agonist selected from EP 0306228 or WO94/05659 can be prepared using the processes described in EP 0306228 and WO94/05659.

When used herein 'Syndrome X' includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidaemia, hyperglycaemia, obesity and the

complications associated with diabetes; the methods and treatments mentioned herein include the above unless specifically stated otherwise.

For the avoidance of doubt, the methods and treatments of this invention also encompass the treatment and/or prophylaxis of any one of or any combination of the following list: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidaemia, hyperglycaemia, obesity and the complications associated with diabetes.

The complications associated with diabetes include cardiovascular disease, especially atherosclerosis, retinopathy, neuropathy and renal disease including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

When used herein the term 'PPAR α agonist' relates to an agonist of the peroxisomal proliferator-activated receptor, suitably the human receptor, of the alpha subtype.

When used herein the term 'PPAR γ agonist' relates to an agonist of the peroxisomal proliferator-activated receptor, suitably the human receptor, of the gamma subtype.

PPAR α and γ agonist activity may be assessed by use of the methodology, or similar methodology, to that disclosed by Lehmann et al : Journal of Biological Chem., 270, 12953-12956 (1995).

In one aspect PPAR α agonist compounds are those which stimulate a PPAR alpha chimeric receptor consisting of the PPAR alpha ligand binding site linked to a suitable reporter gene construct such as luciferase or chloramphenicol acetyltransferase (CAT). This activity can be identified by using the methods outlined by Lehmann et al., *ibid*.

In one aspect PPAR γ agonist compounds are those which stimulate a PPAR γ chimeric receptor containing the PPAR gamma ligand binding site linked to a suitable reporter gene construct such as luciferase or chloramphenicol acetyltransferase (CAT). This activity can be identified by using the methods of Lehmann et al . J Biol. Chem., *ibid*.

Agonists may be proteins or non- proteins.

Suitable agonists are small molecular weight, non-protein compounds.

Also included in the present invention is a method for detecting a compound having both PPAR α and PPAR γ agonist activity.

Suitable methods of detection include determining:

- (a) PPAR α agonist activity by detecting stimulation of a PPAR alpha chimeric receptor consisting of the PPAR alpha ligand binding site linked to a suitable reporter gene construct; and
- 5 (b) PPAR γ agonist activity by detecting stimulation of a PPAR γ chimeric receptor containing the PPAR gamma ligand binding site linked to a suitable reporter gene construct such as luciferase or chloramphenicol acetyltransferase (CAT).

10 A suitable PPAR α chimeric receptor comprises the amino acids of the ligand binding domain, for example amino acids 281-468, of the human PPAR α , fused to amino acids 1-147 (DNA binding domain) of the gal 4 yeast transcription factor.

15 A suitable PPAR γ chimeric receptor comprises the amino acids of the ligand binding domain, for example amino acids 173-476, of the human PPAR γ receptor fused to amino acids 1-147 (DNA binding domain) of the gal 4 yeast transcription factor.

A suitable reporter gene construct is a luciferase or chloramphenicol acetyltransferase (CAT).

A suitable luciferase reporter gene construct contains gal 4 DNA binding elements in HEK-293 cells.

20 Suitable methodology for the said method of detection is as described above.

The present invention also provides an agonist of PPAR α and PPAR γ , for use in the treatment and/or prophylaxis of Syndrome X.

A particular treatment is the prophylaxis of hyperglycaemia.

25 A particular treatment is the treatment of pre-diabetic insulin resistance syndrome and the resulting complications thereof.

Also included is the treatment and/or prophylaxis of hyperglycaemia and/or pre-diabetic insulin resistance syndrome and the resulting complications thereof; providing the said treatment does not include administration of:

30 (S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid; or

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid, for the treatment and/or prophylaxis of:

35 hyperglycaemia, especially in Type II diabetes, hyperlipidaemia, hypertension, cardiovascular disease, especially atherosclerosis and of renal disease, especially

renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease and for the prevention, reversal, stabilisation or retardation of the progression of
5 microalbuminuria to albuminuria.

The present invention also provides an agonist of PPAR α and PPAR γ , for use in the manufacture of a medicament the treatment and/or prophylaxis of Syndrome X, and in particular for the treatment and/or prophylaxis of hyperglycaemia and/or pre-diabetic insulin resistance syndrome and the resulting
10 complications thereof; providing the said treatment does not include administration of:

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid; or
(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-
15 trifluoroethoxy)propanoic acid, for the treatment and /or prophylaxis of: hyperglycaemia, especially in Type II diabetes, hyperlipidaemia, hypertension, cardiovascular disease, especially atherosclerosis and of renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic
20 syndrome, hypertensive nephrosclerosis and end stage renal disease and for the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

This is considered to be the first indication of a compound having agonist activity at both PPAR α and PPAR γ . Other compounds having this dual activity
25 would also be of particular use for the treatment and/or prophylaxis of Syndrome X, including hyperglycaemia and pre-diabetic insulin resistance syndrome and the resulting complications thereof.

Accordingly, in a further aspect the present invention also provides a compound having agonist activity at both PPAR α and PPAR γ .

30 Suitable compounds are unique, in that they are not known to have agonist activity at both PPAR α and PPAR γ or they are novel compounds *per se*.

In one aspect the said compound having agonist activity at both PPAR α and PPAR γ does not include:

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid; or
35

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid.

The invention also provides a compound for use as an agonist of both PPAR α and PPAR γ .

5 The invention further provides the a compound having agonist activity at both PPAR α and PPAR γ for use as an active therapeutic substance; suitably providing that the compound does not include:

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid; or

10 (S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid.

In the above mentioned treatments the active compound is administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

15 Accordingly, the present invention also provides a pharmaceutical composition comprising an agonist of PPAR α and PPAR γ and a pharmaceutically acceptable carrier therefor; suitably providing the said agonist does not include: (S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid; or

20 (S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid.

In addition there is provided a method for treating conditions caused by a requirement for an agonist of both PPAR α and PPAR γ in a human or non-human mammal, which method comprises the administration of an effective, pharmaceutically acceptable, non-toxic amount of an agonist of both PPAR α and PPAR γ .

25 As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

30 Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

5 In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

10 Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

15 Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the above mentioned treatments the active compounds are suitably taken in doses such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of
20 from 0.1 to 6000 mg, and more usually about 1 to 1500 mg, generally about 0.5 to 10 mg. That is in the range of from 1.429×10^{-3} to 85.714 mg/kg/day, more usually about 1.429×10^{-2} to 21.429 mg/kg/day, generally about 7.143×10^{-3} to 0.1429 mg/kg/day.

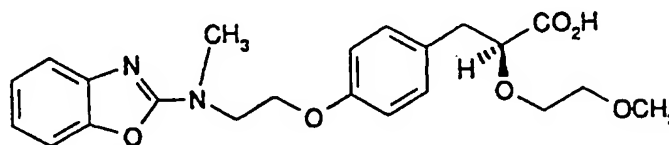
25 No adverse toxicological effects are expected when a compound is administered in accordance with the above mentioned invention.

The activity of the present compounds can be demonstrated using the methods disclosed below. The following Preparations illustrate the preparation of the compounds of formula (I).

PREPARATION OF COMPOUNDS OF FORMULA (I)

Preparation 1: (S)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid

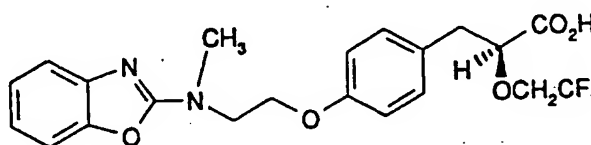
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A solution of [2S, N(1S)]-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide (1.846 g) in a mixture of 1M sulphuric acid (45 mL) and dioxan/water (1:1, 150 mL) was heated at 90°C for 56 hours and then the pH of the mixture was adjusted to pH 3 by addition of aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the organic extracts washed with water, brine, dried (MgSO₄) and evaporated to give an oil. Purification by chromatography on silica gel using a gradient of 1-5% methanol in dichloromethane as eluent gave a foam of 88% e.e. (by HPLC). The product was reacted with (S)-α-methylbenzylamine in acetone, and the resulting salt recrystallised several times from ethyl acetate-hexane before being dissolved in water, acidified with dilute hydrochloric acid and extracted with ethyl acetate which was dried with MgSO₄. Evaporation of the ethyl acetate solution afforded enantiomerically enriched title compound; [α]_D²⁵ -28° (c=0.625, CHCl₃); e.e 94% (by HPLC); [Found M⁺ 414.1791. C₂₂H₂₆N₂O₆ requires M⁺ 414.1791]; ¹H NMR spectrum identical with that described in Example 5.

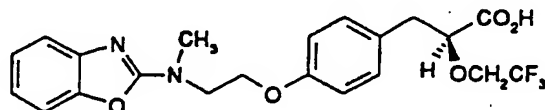
Preparation 2: (S)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid by hydrolysis of amide

30



[2S, N(1S)]-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide (from Procedure 3) was hydrolysed by an analogous procedure to that described in Preparation 1. Purification by chromatography on silica gel using a gradient of 0-5% methanol in dichloromethane as eluent gave the title compound, mp 116-7°C, after trituration with diethyl ether-hexane; $[\alpha]_D^{25}$ -24.6° (c=0.24, CHCl₃); e.e. 95% (by HPLC). [Found C, 57.9; H, 4.7; N, 6.8%; M⁺ 438.1403. C₂₁H₂₁F₃N₂O₅ requires C, 57.5; H, 4.8; N, 6.4%; M⁺ 438.1403]; δ_H (DMSO-d₆) 2.96 (2H,m), 3.22 (3H,s), 3.88 (2H,m), 3.95-4.18 (2H,m), 4.27 (3H,m), 6.8-7.37 (8H,m) and 12.9 (1H,br s, exchanges with D₂O).

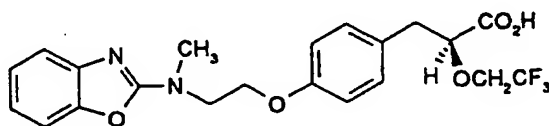
Preparation 3: (S)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic Acid, by Direct Hydrolysis of the Imide



Aqueous sodium hydroxide solution (2.5M, 65 mL, 0.163 mol, 2.3 eq) was added to a stirred solution of [3(2S), 4S]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one (from Procedure 10)(42.5 g, 0.071 mol) in THF (500 mL) and water (125 mL). The mixture was stirred for 20 minutes, the reaction was diluted with water (1 L) and extracted with dichloromethane (3 x 700 mL). These dichloromethane solutions were evaporated and the residue purified by chromatography on silica gel using 5% methanol in dichloromethane as eluent to afford (S)-4-benzyloxazolidin-2-one. The original aqueous solution was acidified to pH 3.5 with dilute hydrochloric acid and re-extracted with dichloromethane (3 x 700 mL). The dichloromethane solutions from the acid extraction were dried (MgSO₄) and evaporated to give a solid. This was recrystallised from dichloromethane-diethyl ether to afford the title compound, mp 119.5-120.5°C. $[\alpha]_D^{25}$ = -31° (c = 2.50, CHCl₃); e.e. 99.6% (by HPLC); [Found C, 57.7; H, 4.7; N, 6.25%; M⁺ (EI) 438.1412. C₂₁H₂₁F₃N₂O₅ requires C, 57.5; H, 4.8; N, 6.4%; M⁺ 438.1403]; δ_H (CDCl₃) 3.05 (1H, dd), 3.13 (1H, dd), 3.31 (3H, s), 3.72 (1H,

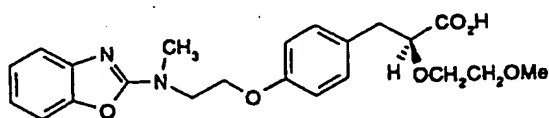
m), 3.89 (2H, m), 4.04-4.14 (3H, m), 4.21 (1H, dd), 6.78 (2H, d), 7.03-7.40 (6H, m) and 11.20 (1H, br, exchanges with D₂O); δ_F (DMSO-d₆) = -72.7 (3F, t, $^3J_{HF}$ 9.3 Hz, CF₃).

5 **Preparation 4: (S)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic Acid by Hydrolysis of Methyl Ester**



- 10 A mixture of (S)-methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoate (1.256 g, 2.8 x 10⁻³ mol), aqueous hydrochloric acid (2.0M, 50 mL) and dioxan (50 mL) was heated at reflux for 7 hours, cooled and concentrated *in vacuo*. The residue was suspended in brine (200 mL) and extracted with ethyl acetate (3 x 300 mL). The combined ethyl acetate solutions were dried (MgSO₄) and evaporated to afford a waxy solid. This solid was triturated with hexane, filtered and dried under vacuum at 65°C to afford the desired product, mp 113-5°C. $[\alpha]_D^{25} = -32^\circ$ (c = 1.02, CHCl₃); e.e. 99.4% (by HPLC); [Found C, 57.25; H, 4.8; N, 6.3%. C₂₁H₂₁F₃N₂O₅ requires C, 57.5; H, 4.8; N, 6.4%]. The ¹H NMR spectrum of this material was identical to that produced in Example 3.

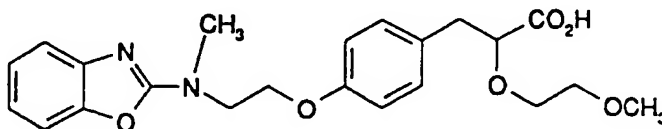
Preparation 5: (S)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic Acid



- 25 (S)-Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoate was hydrolysed in a manner analogous to that described for Example 4. The crude reaction mixture was chromatographed on silica gel using 5% methanol in dichloromethane as eluent to afford the title compound, a gum. $[\alpha]_D^{25} = -27^\circ$ (c = 0.73, CHCl₃); e.e. 99.8% (by HPLC); [Found M⁺ (EI) 414.1779. C₂₂H₂₆N₂O₆ requires M⁺ 414.1791]; δ_H (CDCl₃)

2.90 (1H, dd), 3.15 (1H, dd), 3.33 (3H, s), 3.37 (3H, s), 3.40-3.70 (4H, m), 3.93 (2H, t), 4.05 (1H, dd), 4.21 (2H, t), 6.81 (2H, d) and 6.95-7.40 (6H, m).

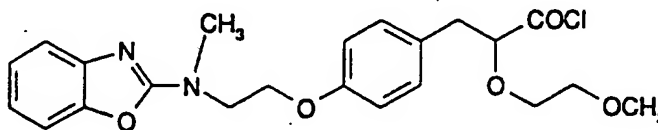
Preparation 6: (±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid



A mixture of methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoate (1.08 g, *Int. Patent Appl., Publication No.* WO 9401420) and sodium hydroxide (253 mg) in methanol:water (1:1, 10 mL) was heated under reflux for 2 hours. After evaporation of the resultant mixture *in vacuo*, the residue was diluted with water, acidified to pH 5 with 2M hydrochloric acid and then extracted with ethyl acetate. Washing of the ethyl acetate extracts with water and drying (MgSO_4) and evaporation gave the title compound as an oil which crystallised on trituration with diethyl ether/hexane. [Found C, 63.8; H, 6.5; N, 7.0%; M^+ 414.1791. $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_6$ requires C, 63.8; H, 6.3; N, 6.8%; M^+ 414.1791]; δ_{H} (CDCl_3) 2.91 (1H, dd), 3.15 (1H, dd), 3.34 (3H, s), 3.38 (3H, s), 3.41-3.69 (4H, m), 3.93 (2H, t), 4.05 (1H, dd), 4.21 (2H, t), 6.80 (2H, d) and 6.83-7.38 (6H m).

Procedure 2

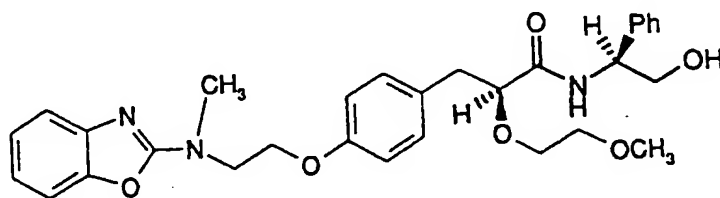
Preparation 7: (±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl chloride



Oxalyl chloride (92 mg) was added to (±)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid (100 mg) in dichloromethane (2 mL). The mixture was stirred at room temperature for

16 hours and evaporated to dryness to give the title compound as a gum which was used without further purification.

- 5 Preparation 8: [2*S*, N(1*S*)]-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide

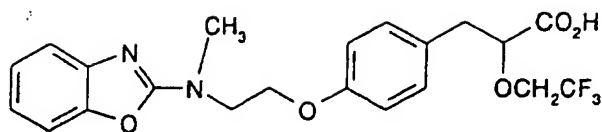


- 10 (±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl chloride was dissolved in dichloromethane (2 mL) and a mixture of (*S*)-2-phenylglycinol (33 mg) and dry triethylamine (37 mg) in dichloromethane (1 mL) added. After stirring for 5 minutes water was added and the mixture
15 extracted with dichloromethane. The organic extracts were washed with water, brine, dried (MgSO₄) and evaporated. The residue was chromatographed on silica gel using a gradient of 10-50% acetone in hexane as eluent to afford firstly [2*R*, N(1*S*)]-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide followed by the
20 desired [2*S*, N(1*S*)]-propanamide title compound as a foam. $[\alpha]_D^{25} -33^\circ$ ($c=1.1$, CHCl₃); 92.6% d.e. (by HPLC); [Found M^+ 533.2526. C₃₀H₃₅N₃O₅ requires M^+ 533.2526]; δ_H (CDCl₃) 2.81 (1H,dd), 3.07 (1H,dd), 3.35 (3H,s), 3.36 (3H,s), 3.48-3.58 (2H,m), 3.52-3.62 (2H,m), 3.71 (1H,dd), 3.82 (1H,dd), 3.94 (1H,dd), 3.93 (2H,t), 4.22 (3H,t), 5.05 (1H,dt), 6.75-7.35 (13H,complex), 7.54
25 (1H,br, exchanges with D₂O).

Procedure 4

Preparation 9: (±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid

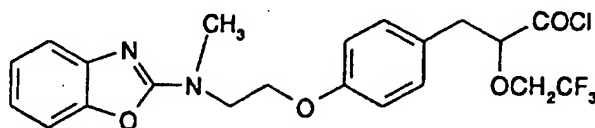
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Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoate (*Int. Patent Appl., Publication No.* WO 9401420) was hydrolysed by an analogous procedure to that described in Preparation 5 to give the title compound as a solid, mp 116-117°C; [Found C, 57.4; H, 4.9; N, 6.4%. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%]; δ_H ($CDCl_3$) 3.03-3.17 (2H,m), 3.29 (3H,s), 3.73-3.83 (1H,m), 3.85 (2H,m), 4.02 (2H,m), 4.04-4.30 (2H,m) and 6.74-7.40 (8H m).

Procedure 5

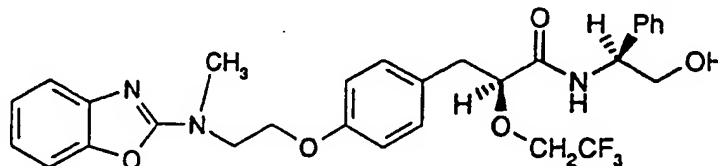
Preparation 10: (\pm)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl chloride



Oxalyl chloride (1.1 mL) was added to a solution of (\pm)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid (1.72 g) in dry benzene (30 mL). The mixture was heated at reflux for 2 hours, cooled and evaporated to dryness to give the title compound as a gum which was used without further purification.

Procedure 6

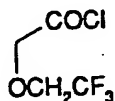
Preparation 11: [2S, N(1S)]-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide



(±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl chloride was reacted with (S)-2-phenylglycinol by an analogous procedure to that described in Procedure 3. Chromatography on silica gel using a gradient of 10-70% ethyl acetate in hexane as eluent afforded firstly

5 [2R, N(1S)]-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide followed by the desired [2S, N(1S)]-propanamide title compound as a foam; $[\alpha]_D^{25} +14^\circ$ (c=0.5, MeOH); 99% d.e. (by HPLC); [Found M^+ 557.2136. $C_{29}H_{30}F_3N_3O_5$ requires M^+ 557.2138]; δ_H ($CDCl_3$) 2.35 (1H, br, exchanges with D_2O), 2.91 (1H, dd), 3.13 (1H, dd), 3.36 (3H, s), 3.70-3.87 (2H, m), 3.84 (2H, d), 3.95 (2H, t), 4.12 (1H, dd), 4.22 (2H, t), 5.01 (1H, m), 6.75 (2H, d), 6.97 (1H, br s, exchanges with D_2O) and 7.01-7.36 (11H, complex).

15 Preparation 12: (2,2,2-Trifluoroethoxy)ethanoyl Chloride



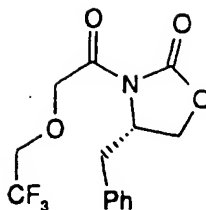
A solution of oxalyl chloride (20 mL, 0.23 mol, 1.15 eq) in dry dichloromethane (50 mL) was added dropwise at room temperature, with stirring, to a solution of

20 (2,2,2-trifluoroethoxy)ethanoic acid (*Int. Patent Appl., Publication No. WO 87/07270*, 31.6 g, 0.2 mol) and N,N-dimethylformamide (5 drops) in dry dichloromethane (400 mL). The mixture was stirred for an additional hour, then heated under reflux for 2 hours, cooled and the bulk of the solvent removed by distillation (bp 40-45°C/760 mm Hg). The residue was transferred to a Claisen

25 distillation flask and the remaining solvent and oxalyl chloride removed by distillation (bp 45-60°C/760 mm Hg). Vacuum distillation of the residue then afforded the product, bp 50-55°/25-32 mm Hg. δ_H ($CDCl_3$) 4.00 (2H, q, $^3J_{HF}$ 8.3) and 4.57 (2H, s).

30 Procedure 8

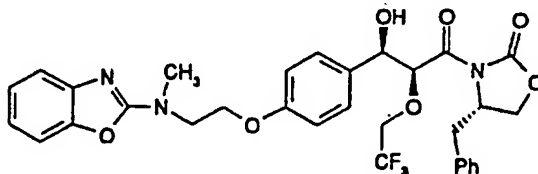
Preparation 13: (4S)-4-Benzyl-3-[2-(2,2,2-trifluoroethoxy)ethanoyl]oxazolidin-2-one



(4S)-4-Benzylloxazolidine-2-one (5.21 g, 0.029 mol) was dissolved in dry THF (60 mL) and cooled to -70°C under argon. *n*-Butyllithium (18.4 mL, 1.6 M solution in hexane, 1.1 eq) was added over 10 minutes and the resulting mixture stirred at -70°C for 20 minutes. A solution of (2,2,2-trifluoroethoxy)ethanoyl chloride (5.19 g, 1 eq) in dry THF (60 mL) was added over 10 minutes, the mixture stirred at -70°C for a further 30 minutes then allowed to warm to room temperature overnight. The reaction was quenched by addition of brine (20 mL) and concentrated *in vacuo*. The residue was diluted with brine (300 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were dried (MgSO₄), evaporated and the residue chromatographed on silica gel with dichloromethane as eluent to give the product as an oil. $[\alpha]_D^{25} = +48^\circ$ (c = 2.55, CHCl₃); e.e. 100% (by HPLC); [Found (CI, Ammonia) MH⁺ 318.0934. C₁₄H₁₄NO₄F₃ requires MH⁺ 318.0953]; δ_H (CDCl₃) 2.82 (1H, dd), 3.34 (1H, dd), 4.02 (2H, q, $^3J_{HF}$ 8.6), 4.30 (2H, m), 4.69 (1H, m), 4.84 (2H, s) and 7.15-7.40 (5H, m); δ_F (CDCl₃) = -74.8 (3F, t, $^3J_{HF}$ 8.6, CF₃).

Procedure 9

Preparation 14: [3(2S, 3R), 4S]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzylloxazolidin-2-one



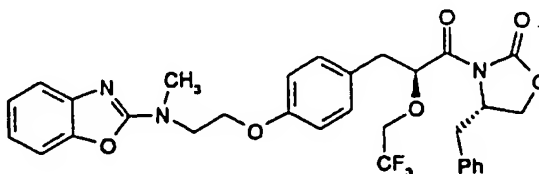
(4S)-4-Benzyl-3-[2-(2,2,2-trifluoroethoxy)ethanoyl]oxazolidin-2-one (31.7 g, 0.1 mol) was dissolved in dry dichloromethane (300 mL) under argon and cooled to -78°C (internal temperature of solution), using liquid nitrogen/acetone as the cooling medium. Triethylamine (16.72 mL, 1.2 eq) was added, followed by the

slow addition, over approximately 10 minutes, of di-*n*-butylboron triflate (Aldrich Chemical Company, 1.0M solution in dichloromethane, 110 mL, 1.1 eq) such that the reaction temperature was maintained below -70°C. The mixture was stirred at -78°C for 50 minutes, then the cooling bath was replaced with an ice bath and the mixture stirred at 0°C for an additional 50 minutes before being recooled to -78°C. A solution of 4-[2-[N-(2-benzoxazolyl)-N-methylamino]-ethoxy]benzaldehyde (29.6 g, 1.0 eq) in dry dichloromethane (220 mL), precooled to -50°C, was added over *ca.* 12 minutes, such that the reaction temperature was maintained below -70°C. The resulting mixture was stirred at -78°C for 30 minutes, then warmed from -78°C to 0°C over 60 minutes along a linear gradient (warming rate ~ 1.3°C.min⁻¹) and stirred at 0°C for a further 75 minutes. The reaction mixture was poured into a quenching solution of methanol (500 mL), pH 7 phosphate buffer (250 mL) and hydrogen peroxide (27.5% w/v, 110 mL) and stirred vigorously for 30 minutes. Water (4 L) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 x 1 L). The dichloromethane solutions were recombined with the original dichloromethane layer from the reaction mixture and this organic solution was then washed with water (2 L) and brine (2 L), dried (MgSO₄) and evaporated to afford a foam. ¹H NMR of this crude reaction mixture suggested a mixture of the desired aldol product (3 diastereoisomers, comprising 95% major diastereoisomer) and starting materials. The crude mixture was chromatographed on silica gel using a gradient elution comprising 15% ethyl acetate in dichloromethane initially (until the desired product began to elute) and rising to 50% ethyl acetate in dichloromethane to complete the elution of the desired product. Unreacted imide and aldehyde were recovered from the early fractions, followed by a quantity of impure product and then the title compound (comprising 2 diastereoisomers, ratio 97.8:2.2 by NMR). [α]_D²⁵ = +45° (c = 2.82, CHCl₃). [Found (EI) M⁺ 613.2042. C₃₁H₃₀F₃N₃O₇ requires M⁺ 613.2036]; δ _H (CDCl₃, only major diastereoisomer is recorded) 2.75 (1H, dd), 2.90 (1H, d, exchanges with D₂O), 3.25 (1H, dd), 3.34 (3H, s), 3.80-4.00 (5H, m), 4.07 (1H, dd), 4.24 (2H, t), 4.45 (1H, m), 4.99 (1H, apparent t), 5.48 (1H, d), 6.85 (2H, d) and 6.95-7.40 (11H, m); δ _F (CDCl₃) = -74.7 (3F, t, ³J_{HF} 8.5, CF₃). The minor diastereoisomer in the purified product was identified as the [3(2S, 3S), 4S]-diastereoisomer.

Procedure 10

Preparation 15: [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one by Dehydroxylation

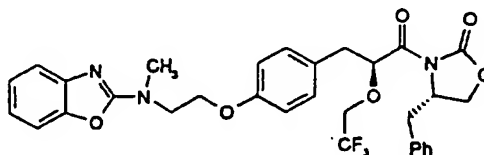
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Triethylsilane (120 mL, 0.75 mol) was added over 5 minutes to a stirred, ice cooled solution of [3(2*S*, 3*R*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one (46.23 g, 7.5 x 10⁻² mol) in trifluoroacetic acid (650 mL). The mixture was stirred at 0°C for 1 hour, then at room temperature for a further 60 hours. The bulk of the solvent and residual triethylsilane was removed by rotary evaporation, firstly at 40 mm Hg and finally at ~5 mm Hg. The residue was dissolved in dichloromethane (800 mL) and water (800 mL), then stirred vigorously during the cautious addition of solid sodium bicarbonate (~29 g) (frothing !) until the pH of the aqueous layer was pH 7. The layers were separated and the aqueous layer was extracted with dichloromethane (800 mL). The combined dichloromethane layers were washed with water (600 mL), dried (MgSO₄) and evaporated. The residue was triturated with hot hexane and the resulting solid collected by filtration. Recrystallisation from diethyl ether-hexane afforded the title compound, mp 107-109°C, a single diastereoisomer by ¹H NMR spectroscopy. [α]_D²⁵ = +38° (c = 1.51, CHCl₃); [Found C, 62.1; H, 4.9; N, 7.2%; M⁺ (EI) 597.2089. C₃₁H₃₀N₃O₆F₃ requires C, 62.3; H, 5.1; N, 7.0%; M⁺ 597.2087]; δ_H (CDCl₃) 2.82 (1H, dd), 2.96 (1H, dd), 3.04 (1H, dd), 3.32 (1H, dd), 3.34 (3H, s), 3.70 (1H, m), 3.88 (1H, m), 3.94 (2H, t), 4.12 (1H, m), 4.18 (1H, m), 4.25 (2H, t), 4.57 (1H, m), 5.34 (1H, dd), 6.82 (2H, d) and 7.00-7.35 (11H, m); δ_F (CDCl₃) = -74.8 (3F, t, ³J_{HF} 8.6, CF₃).

Procedure 11

Preparation 16: [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one via Diastereoisomer Separation



5

(*S*)-4-Benzyloxazolidin-2-one (0.291 g, 1.64 x 10⁻³ mol) was dissolved in dry THF (10 mL) and the resulting solution cooled to -70°C under argon. *n*-Butyl lithium (1.6M in hexane, 1.03 mL, 1.64 x 10⁻³ mol) was added and the mixture was stirred at -70°C for 10 minutes prior to the addition of a solution of (±)-3-[4-

10

2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl chloride (prepared from 0.36 g of the acid by Procedure 5, above) in dry THF (15 mL). The reaction was stirred and allowed to warm to room temperature overnight before being diluted with water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined ethyl acetate layers were washed with water (200 mL) and brine (200 mL), dried (MgSO₄) and evaporated to give a brown gum. This was chromatographed on silica gel using a gradient of 35% to 50% ethyl acetate in hexane as eluent to afford firstly the (*R*, *S*)-diastereoisomer, followed by the title compound, a foam. This material was spectroscopically

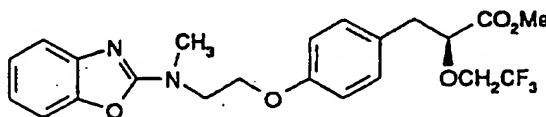
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Procedure 12

Preparation 17: (*S*)-Methyl 3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoate

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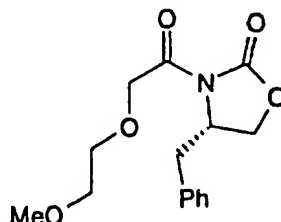
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A solution of sodium methoxide [prepared from sodium hydride (60% dispersion in mineral oil, 138 mg, 3.41 x 10⁻³ mol) dissolved in dry methanol (3.5 mL)] was added to an ice cooled and stirred suspension of [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-

propanoyl]-4-benzylloxazolidin-2-one (1.879 g, 3.1×10^{-3} mol) in dry methanol (100 mL). The mixture was stirred at 0°C for a total of 20 minutes, then the reaction was quenched by the addition of dilute aqueous hydrochloric acid (2.0M, 1.75 mL) and concentrated *in vacuo*. The residue was suspended in water (100 mL), extracted with ethyl acetate (3 x 200 mL) and the combined ethyl acetate solutions washed with brine (500 mL), dried (MgSO₄) and evaporated. The resulting gum was chromatographed on silica gel using 4% ethyl acetate in dichloromethane as eluent to afford the product as a clear gum. $[\alpha]_D^{25} = -17^\circ$ (c = 1.24, CHCl₃); [Found (EI) M⁺ 452.1561. C₂₂H₂₃N₂O₅F₃ requires M⁺ 452.1559]; e.e. 100% (by HPLC); δ_H (CDCl₃) 3.02 (2H, m), 3.34 (3H, s), 3.65 (1H, m), 3.72 (3H, s), 3.94 (2H, t), 4.00 (1H, m), 4.13 (1H, dd), 4.24 (2H, t), 6.80 (2H, d) and 6.96-7.40 (6H, m).

Procedure 13

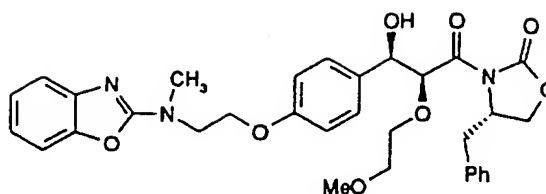
Preparation 18: (4S)-4-Benzyl-3-[2-(2-methoxyethoxy)ethanoyl]oxazolidin-2-one



The title compound was prepared from 2-(2-methoxyethoxy)ethanoyl chloride by a method analogous to that described in Procedure 8. Chromatography on silica gel using a gradient of 70-80% diethyl ether in hexane as eluent afforded the product as a gum. $[\alpha]_D^{25} = +54^\circ$ (c = 2.70, CHCl₃); [Found (EI) M⁺ 293.1263. C₁₅H₁₉NO₅ requires M⁺ 293.1264]; δ_H (CDCl₃) 2.81 (1H, dd), 3.33 (1H, dd), 3.41 (3H, s), 3.63 (2H, t), 3.78 (2H, t), 4.25 (2H, m), 4.70 (1H, m), 4.74 (1H, d), 4.76 (1H, d) and 7.10-7.40 (5H, m).

Procedure 14

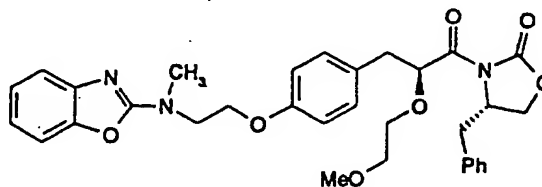
Preparation 19: [3(2S, 3R), 4S]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2-methoxyethoxy)propanoyl]-4-benzylloxazolidin-2-one



The title compound was prepared from (4*S*)-4-benzyl-3-[2-(2-methoxyethoxy)ethanoyl]oxazolidin-2-one by a method analogous to that described in Procedure 9. The crude reaction mixture was chromatographed on silica gel using a gradient of 15-40% ethyl acetate in dichloromethane to afford the product as a gum (comprising 2 diastereoisomers, ratio >99:1 by ¹H NMR). $[\alpha]_D^{25} = +49^\circ$ ($c = 1.14$, CHCl₃). [Found (FAB, NOBA/Na) MH⁺ 590.2472. C₃₂H₃₅N₃O₈ requires MH⁺ 590.2502]; δ_H (CDCl₃, only major diastereoisomer is recorded) 2.71 (1H, dd), 3.25 (1H, dd), 3.31 (3H, s), 3.35 (3H, s), 3.56 (2H, m), 3.72 (2H, m), 3.78 (1H, d, exchanges with D₂O), 3.85-4.00 (4H, m), 4.22 (2H, t), 4.31 (1H, m), 4.89 (1H, dd), 5.42 (1H, d), 6.83 (2H, d) and 6.95-7.40 (11H, m); The minor diastereoisomer in the purified product was identified as the [3(2*S*, 3*S*), 4*S*]-diastereoisomer.

15 Procedure 15

Preparation 20: [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one



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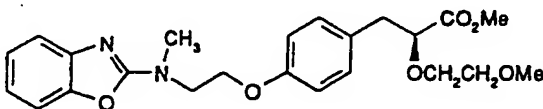
[3(2*S*, 3*R*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one (0.561g) was reacted with triethylsilane for 6.25 hrs in a manner similar to that described for Procedure 10. The reaction mixture was diluted with water (200 mL) and dichloromethane (200 mL) and solid sodium bicarbonate was added cautiously until the aqueous layer showed pH 6.5. The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 300 mL) and the combined

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dichloromethane solutions were washed with brine (400 mL), dried (MgSO_4) and evaporated. The residue was chromatographed on silica gel using 35% ethyl acetate in dichloromethane as eluent to afford the title compound, a gum, as a single diastereoisomer by ^1H NMR. $[\alpha]_{\text{D}}^{25} = +45^\circ$ ($c = 1.39$, CHCl_3); [Found M^+ (EI) 573.2473. $\text{C}_{32}\text{H}_{35}\text{N}_3\text{O}_7$ requires M^+ 573.2475]; δ_{H} (CDCl_3) 2.76 (1H, dd), 2.94 (2H, m), 3.30 (3H, s), 3.33 (4H, m), 3.40-3.70 (4H, m), 3.93 (2H, t), 4.00 (1H, dd), 4.12 (1H, dd), 4.22 (2H, t), 4.52 (1H, m), 5.31 (1H, dd), 6.79 (2H, d) and 6.90-7.40 (11H, m).

10 Procedure 16

Preparation 21: (*S*)-Methyl 3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoate



- 15 [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl]-4-benzylloxazolidin-2-one was reacted with sodium methoxide in a manner analogous to that described in Procedure 12. The crude reaction mixture was chromatographed on silica gel using 20% isohexane in diethyl ether as eluent to afford the title compound, a gum. $[\alpha]_{\text{D}}^{25} = -12^\circ$ ($c =$
- 20 1.26, CHCl_3); [Found (EI) M^+ 428.1974. $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_6$ requires M^+ 428.1948]; e.e. >99.8% (by HPLC); δ_{H} (CDCl_3) 2.95 (2H, m), 3.29 (3H, s), 3.34 (3H, s), 3.35 (3H, m), 3.69 (4H, m), 3.93 (2H, t), 4.05 (1H, dd), 4.23 (2H, t) and 6.75-7.40 (8H, m).

DEMONSTRATION OF EFFICACY OF COMPOUNDS

1) Determination of hPPAR α and hPPAR γ agonist activity

5 Compound agonist effects at human PPAR α and PPAR γ were assessed using a transactivation reporter gene assay, based on that described by Lehman et al. (1995) J Biol Chem 270, 12953-12956.

Results: Efficacy of (S)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl] 2-(2, 2, 2-trifluoroethoxy)propanoic acid at hPPAR α and hPPAR γ

10 EC₅₀ for activation of human PPAR α is = 2500nM
EC₅₀ for activation of human PPAR γ is = 70nM

2) Determination of compound efficacy on blood glucose and plasma lipids in the C57 Bl/KsJ db/db mouse

15 The genetically diabetic C57 Bl/KsJ db/db mouse displays a severe form of non insulin dependent diabetes mellitus in that it develops a profound hyperglycaemia at about 8 weeks of age. This is paralleled by glycosuria and polyuria with a compensatory increase in water intake. Circulating serum triglycerides and free fatty acids are also elevated.

20 Compounds are administered by dietary admixture (powdered RM3 diet) for 14 days and blood glucose measured in samples taken from the tail vein of conscious non-fasted mice at appropriate intervals during the treatment period. After the 14 day treatment period, mice are killed by cervical dislocation and blood obtained from the severed jugular veins. Triglyceride and non-esterified fatty acids are measured in samples of serum obtained by centrifugation.

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Efficacy of (S)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl] 2-(2,2,2-trifluoroethoxy)propanoic acid on blood glucose in the diabetic mouse

		Control	Treated
EXPT I			
	Blood glucose (mmol/l)		
	pre-dose post dose (13 days)	15.5 ± 3.7 34.0 ± 7.9	15.6 ± 4.0 ***11.0 ± 3.6
EXPT II	Blood glucose (mmol/l)		
	pre-dose	16.5 ± 2.9	16.2 ± 4.3
	Day 1	17.2 ± 3.7	14.1 ± 3.7
	Day 2	19.9 ± 2.7	**15.0 ± 3.4
	Day 3	20.2 ± 3.9	***12.2 ± 5.1
	Day 5	21.2 ± 1.9	***11.3 ± 3.6
	Day 7	23.4 ± 2.0	***11.7 ± 3.7

Results are mean ± SD (n = 9-10 per group). ** p<0.01; *** p<0.001 vs controls.

5 Effect of (S)-3-[4-[2-[N-(2-Benzoxazolyl)-Nmethylamino]ethoxy]phenyl] 2-(2,2,2-trifluoroethoxy)propanoic acid on serum lipids in the genetically diabetic mouse.

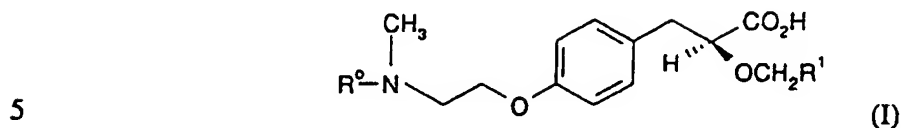
Parameter	Control	Treated (0.3 umol/kg body wt)
Serum non-esterified fatty acids (mmol/l)	2.58 ± 0.45	***1.28 ± 0.15
Serum triglycerides (mmol/l)	3.78 ± 1.34	***2.58 ± 0.45

Parameters were measured in samples taken after 14 days of treatment (dietary admixture). Values are mean ± SD (n=9). *** p<0.001 versus controls.

Claims:

1. A method for the treatment and/or prophylaxis of Syndrome X in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically effective amount of an agonist of PPAR α and PPAR γ , or a pharmaceutically acceptable derivative thereof, to a human or non-human mammal in need of such treatment.
2. A method according to claim 1, wherein the agonist of PPAR α and PPAR γ is the same compound.
3. A method according to claim 1 or claim 2, for the treatment and/or prophylaxis of hyperglycaemia.
4. A method according to any one of claims 1 to 3, for the treatment of pre-diabetic insulin resistance syndrome and the resulting complications thereof.
5. A method for the treatment and/or prophylaxis of hyperglycaemia and/or pre-diabetic insulin resistance syndrome and the resulting complications thereof in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically effective amount of an agonist of PPAR α and PPAR γ , or a pharmaceutically acceptable derivative thereof, to a human or non-human mammal in need thereof; providing the method does not include the administration of:
(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid; or
(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid, for the treatment and /or prophylaxis of:
hyperglycaemia, especially in Type II diabetes, hyperlipidaemia, hypertension, cardiovascular disease, especially atherosclerosis and of renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease and for the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

6. A method according to any one of claims 1 to 5, wherein the PPAR α and γ agonist is a compound of formula (I):



or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein R⁰ represents 2-benzoxazolyl or 2-pyridyl and R¹ represents CH₂OCH₃ or CF₃.

- 10 7. A method according to claim 5, wherein R⁰ represents 2-benzoxazolyl and R¹ represents CH₂OCH₃ or CF₃.
8. An agonist of PPAR α and PPAR γ , for use in the treatment and/or prophylaxis of Syndrome X.
- 15 9. An agonist of PPAR α and PPAR γ , for use in the manufacture of a medicament for the treatment and/or prophylaxis of Syndrome X.
10. A compound having agonist activity at both PPAR α and PPAR γ .
- 20 11. A compound having agonist activity at both PPAR α and PPAR γ for use as an active therapeutic substance.
12. A pharmaceutical composition comprising an agonist of PPAR α and PPAR γ and a pharmaceutically acceptable carrier therefor.
- 25 13. A method for detecting a compound having both PPAR α and PPAR γ agonist activity, which method comprises determining:
- 30 (a) PPAR α agonist activity by detecting stimulation of a PPAR alpha chimeric receptor consisting of the PPAR alpha ligand binding site linked to a suitable reporter gene construct; and

(b) PPAR γ agonist activity by detecting stimulation of a PPAR γ chimeric receptor containing the PPAR gamma ligand binding site linked to a suitable reporter gene construct.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 97/00058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/42 A61K31/44 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 04261 A (SMITHKLINE BEECHAM) 15 February 1996 see the whole document ---	1-12
P,X	WO 96 04260 A (SMITHKLINE BEECHAM) 15 February 1996 cited in the application see the whole document ---	1-12
P,X	J. MED. CHEM., vol. 39, 2 February 1996, pages 665-668, XP000613613 T.M. WILLSON ET AL.: "THE STRUCTURE-ACTIVITY RELATIONSHIP BETWEEN PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONISM AND THE ANTIHYPERGLYCEMIC ACTIVITY OF THIAZOLIDINEDIONES" see the whole document --- -/-	1-3,5, 8-12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

21 April 1997

Date of mailing of the international search report

23.05.97

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Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/00058

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA, vol. 21, no. 2, 1992, pages 329-350, XP000605976 J.H. KARAM: "TYPE II DIABETES AND SYNDROME X" see the whole document, in particular pages 344-347 ---	1-5,8-12
X	ACTA MED. SCAND., vol. 201, 1977, pages 563-566, XP000671179 S.C. ENGER ET AL.: "THE EFFECT OF CLOFIBRATE ON GLUCOSE TOLERANCE, INSULIN SECRETION, TRIGLYCERIDES AND FIBRINOGEN IN PATIENTS WITH CORONARY HEART DISEASE" see the whole document ---	1-5,8-12
X	CLINICAL TRIALS JOURNAL, vol. 14, no. 1, 1977, pages 15-22, XP000671175 S.I. CSÖGÖR ET AL.: "CLINICAL OBSERVATION AND TRIAL OF HYPOGLYCAEMIC EFFECTS OF CLOFIBRATE" see the whole document ---	1-3,5, 8-12
X	US 5 130 333 A (PAN ET AL.) 14 July 1992 see column 4, line 25 - line 45; example 3 ---	1-5,8-12
A	BIOL. CELL, vol. 77, 1993, pages 67-76, XP000613577 C. DREYER ET AL.: "POSITIVE REGULATION OF THE PEROXISOMAL BETA-OXIDATION PATHWAY BY FATTY ACIDS THROUGH ACTIVATION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPAR)" see the whole document ---	1-5,8-12
A	CELL, vol. 79, 1994, pages 1147-1156, XP000577080 P. TONTONNOZ ET AL.: "STIMULATION OF ADIPOGENESIS IN FIBROBLASTS BY PPARGAMMA2, A LIPID-ACTIVATED TRANSCRIPTION FACTOR" see the whole document ---	1-5,8-12
X	EP 0 302 481 A (CENTURY LABORATORIES INC.) 8 February 1989 see the whole document ---	1-3,5, 8-12

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 97/00058

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 22, 1995, pages 12953-12956, XP000577082 J.M. LEHMAN ET AL.: "AN ANTIDIABETIC THIAZOLIDINEDIONE IS A HIGH AFFINITY LIGAND FOR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPARGAMMA)" cited in the application see the whole document ---</p>	8-13
X	<p>CELL, vol. 83, 1995, pages 813-819, XP000575884 S.A. KLIWER ET AL.: "A PROSTAGLANDIN J2 METABOLITE BINDS PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AND PROMOTES ADIPOCYTE DIFFERENTIATION" see the whole document ---</p>	8-11
A	<p>WO 94 01420 A (SMITHKLINE BEECHAM) 20 January 1994 cited in the application see the whole document -----</p>	1-12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 97/00058

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-7
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: 1-5, 8-13
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
A compound cannot be sufficiently characterised by its pharmacological pro-
file or its mode of action as it is done by the expression like "PPAR-alpha
and PPAR-gamma agonist". Therefore the search was limited to the compounds
specifically mentioned in the description.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No

PCT/EP 97/00058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9604261 A	15-02-96	AU 3382695 A	04-03-96
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		PL 307087 A	02-05-95
		SK 695 A	11-07-95
		ZA 9304730 A	03-01-95
		HU 71247 A	28-11-95



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/42, 31/44, 31/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/25042</p> <p>(43) International Publication Date: 17 July 1997 (17.07.97)</p>
<p>(21) International Application Number: PCT/EP97/00058</p> <p>(22) International Filing Date: 7 January 1997 (07.01.97)</p> <p>(30) Priority Data: 9600464.3 9 January 1996 (09.01.96) GB</p> <p>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p> <p>(72) Inventor; and</p> <p>(75) Inventor/Applicant (for US only): SMITH, Stephen, Alistair [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).</p> <p>(74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published</p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: USE OF AN AGONIST OF PPAR-ALPHA AND PPAR-GAMMA FOR THE TREATMENT OF SYNDROM X</p> <p>(57) Abstract</p> <p>A method for the treatment and/or prophylaxis of Syndrome X in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically effective amount of an agonist of PPARα and PPARγ, or a pharmaceutically acceptable derivative thereof, to a human or non-human mammal in need of such treatment, and certain compound for use in such method.</p>		

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BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

